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REITER'S SYNDROME — REVIEW

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"Reiter's syndrome," the classical triad of non-gonococcic urethritis, conjunctivitis and arthritis is no longer considered a rarity. Because of its multiple system involvement, members of several specialty groups have written on this subject. In recent years mucocutaneous lesions have been recognized with increasing frequency. Reiter's syndrome has become a tetrad complex. Although Reiter has received eponymic laurels for his description of this syndrome, several others have made earlier contributions. Indeed, Manson-Bahr[1] states that Caelius Aurelianus, a fifth century physician, was keenly aware of the post-dysenteric state and termed it "rheumatismus intestinalis cum ulcere." In 1818 and 1836, Sir Benjamin Brodie[2] described six patients with the triad of urethral discharge, arthritis and inflammation of the eyes. These patients undoubtedly had "Reiter's syndrome," and there is little question of the priority of Brodie's report.

Launois[3] in 1899 gave an extensive account of the relapsing nature of this disease. In his patient he described skin lesions consistent with keratodermia blennorrhagica. These lesions appeared after a prolonged attack of urethritis, arthritis, and subsequently iritis. His failure to find the gonococcus in this patient suggested to him a different etiology for this disease process. Waelsch[4] in 1916 reported on forty-five cases of abacterial urethritis. One patient developed rheumatic pains of the knees and ankles, while a second patient experienced bilateral conjunctivitis two days after the onset of the urethral discharge. Although Waelsch did not recognize the triad as an entity, he did establish the non-gonococcal nature of some cases of venereal urethritis. He considered conjunctivitis and arthritis as complications of a non-bacterial urethritis. During the same year, Hans Reiter[5] described in a German officer the symptom complex of urethritis, conjunctivitis and arthritis which followed a bout of abdominal pain and diarrhea. Gonococci could not be demonstrated in the purulent urethral discharge. However, Reiter did isolate a spirochete from the blood of the patient which he believed was the etiologic agent. He called the spirochete, Spirochaeta forans, and the disease "Spirochaetosis Arthritica."

Fiessinger and Leroy[6] in France during the same year described an identical symptom complex and attributed it to bacillary dysentery. In 1917 Macfie[7] reported a native of the Gold Coast with a hemorrhagic urethral discharge which contained a large number of spirochaetes. This was associated with arthritic pains and severe bilateral iritis. With galyl and mercury treatment Macfie reported a rapid and favorable response.

The first article on this subject in the English literature was by Fruhwald[8] in 1928. It was not until 1942 that the first American study by Bauer and Engleman[9]

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was reported. They mentioned their six patients with this syndrome and wrote in detail concerning one of them. The first reported synovial tissue biopsy findings were obtained from this patient. During and shortly after the Second World War a number of excellent studies, reports and reviews on this syndrome appeared[10–23]. Reiter's[22] recent review and extensive chronological bibliography dealing with all published articles on this subject is worthy of note.

Etiology and Pathogenesis

Much work has been done to establish the etiology of Reiter's syndrome, but up to the present time no definite causative organism has been found. Reiter's claim that it was due to a spirochaete was not confirmed by later investigators. The fact that there appear to be two forms of the syndrome, namely, the venereal and the post-dysenteric, has increased the confusion concerning its etiology. A number believe this syndrome is associated with bacillary dysentery. Young and McEwen[24] reported on 10 cases of urethritis and arthritis among 176 cases of bacillary dystentery; seven of these patients had the complete triad. Although these authors attributed the disease to the dysentery infection stool cultures were negative for the dysentery organisms, and serum agglutination titers against dysentery organisms were never markedly elevated.

Paronen[15] likewise believes the dysentery bacillus to be the causative factor. In his excellent monograph he discusses 344 cases (310 males and 34 females) which followed an epidemic of Flexner dysentery in Finland. He estimated that approximately 2% of the patients affected with dysentery during this extensive epidemic presented Reiter's syndrome. However, in this series only 70% manifested the complete triad; approximately 25% had two of the essential symptoms and 5% had only one component. Thus the complete classical syndrome was not established in 30% of his cases. In these the partial or incomplete syndrome existed. Paronen was unable to demonstrate positive serum agglutination reactions for typhoid, paratyphoid, typhus, and brucella. The gonococcal complement fixation test was negative on every one of the 219 patients on whom it was done. Sixty-one of 132 examined sera agglutinated a Flexner A+ D+ WX suspension in titers of 1:80-1:640. Eight positive results were obtained on the aspirated joint fluids of twenty-four patients.

Manson-Bahr[1] has described a varying incidence of post-dystenteric arthritis in bacillary dysentery. The Doberitz epidemic of 1900 in Germany resulted in a 3.75% incidence of arthritis while in a similar epidemic on the Fiji Islands during 1897 arthritis occurred in 10%. However, Short[25] in a study of 1,120 cases of bacillary dysentery occurring in the Mediterranean area during World War II, found no one with arthritis, while in 10 cases of Reiter's syndrome he found no evidence of active or latent Shigella infection. He suggested, as have others, that the dysentery can activate or provide a portal of entry for the etiologic agent of Reiter's syndrome and that post-dysenteric arthritis may be due to a secondary invader rather than to Shigella itself.

Harkness[16] and Ford[19] believe that Reiter's syndrome is usually of venereal origin. Similar opinion is held by Lovgren and Masreliez[26]. Although they recognize the post-dysenteric form, they believe the etiologic agent is the same, but that the portal of entry is different. According to this hypothesis, both forms are due to a single etiologic agent. Gonococcal infection, active or latent, has long been assumed by many authors to be the cause of the veneral form of Reiter's syndrome. Harkness[16] challenged this point of view. He observed that certain patients with a gonococcal urethritis developed the same type of joint disease as presented by others with non-specific urethritis. The advent of penicillin therapy has shown that the two diseases sometimes coexist. The highly sensitive gonococcus can readily be eradicated with penicillin, yet this treatment which "cures" the specific urethritis does not prevent the development or affect the course of this syndrome. Harkness believes that the venereal and the epidemic forms are due to a virus or to pleuropneumonia-like organisms. He found inclusion bodies in scrapings from the

urethra, conjunctiva, and the skin of a patient with Reiter's syndrome. To Harkness these elementary bodies represent either virus groupings, or a phase in the life cycle of an unknown new organism.

Dunham[27] and his collaborators have reported an interesting study suggesting a viral etiology for this condition. They isolated a filterable agent from the urethral and conjunctival discharges of a patient with Reiter's syndrome. This proved to be pathogenic for mice. The urethral and conjunctival secretions from this patient were separately inoculated into the allantoic fluid of twelve day embryonated eggs which were incubated for forty-eight hours. The pooled allantoic fluid from each series was then filtered through a Seitz E.K. filter. Twenty mice were inoculated intraperitoneally with 0.1 ml. of a saline solution of the allantoic filtrate from the urethral discharge and a similar number of mice were inoculated with allantoic filtrate from the eye secretion. Ten mice served as controls for each group. Slightly over 60% of the inoculated animals developed conjunctivitis but none of the control animals showed this reaction. Joint and genitourinary findings were not described. These interesting studies warrant further study and confirmation. Weinberger[17] et al, using a different procedure, were unable to demonstrate virus growth in embryonated eggs after their inoculation with the conjunctival and urethral secretions from their patients.

In recent years the organisms belonging to the pleuropneumonia group ("L" organisms) have assumed prominence as the possible etiologic agent of Reiter's syndrome. Sabin[28] relates that Nocard and Roux in 1898 isolated the first member of this group from cattle which had pleurisy, pneumonia and arthritis to some degree. In 1923 Bridre and Donatien demonstrated a similar organism isolated from sheep and goats suffering from agalactia, an interesting syndrome consisting of mastitis with suppression of lactation, chronic arthritis, keratitis, and vesiculopustular skin eruptions.

It was soon demonstrated that experimental polyarthritis could be established in rats by another organism of this group[29]. Sabin[30] with a different strain of pleuropneumonia-like organism produced a chronic, proliferative arthritis in mice. This arthritis clinically and pathologically bore a great resemblance to human rheumatoid arthritis. There was typical "rheumatoid" fusiform swelling of the involved joints and in the later stages ankylosis developed. There likewise existed a therapeutic similarity between these two forms of arthritis. Several investigators found that various gold compounds when tested against the experimentally induced mouse arthritis had a similar degree of effectiveness as in humans[31–35].

Following brilliant experimental studies, attention was soon focused on the possibility that this organism might be the cause of some forms of human arthritis. The search for "L" organisms was on. Unfortunately, these organisms were not established as the cause of rheumatic fever or rheumatoid arthritis[36–37]. The line of investigation did lead to a new area. Dienes and Edsall[38] in 1937 had isolated "L" organisms in pure culture from a female patient with a suppurating Bartholin's gland. Further studies by Dienes[39] in 1940 demonstrated that about one-third of all women with chronic pelvic infections harbored pleuropneumonia-like organisms in their cervical secretions. In apparently normal females, Beveridge, Campbell and Lind[40] were able to obtain positive cultures only in 17% of 101 patients. The incidence of "L" organisms is apparently quite high in the female population. Its relationship to Reiter's syndrome rests on inferential evidence.

Only 9 of 58 women from whom Dienes[41] obtained positive cultures had joint complaints. The majority had chronic rather than acute forms of arthritis. However, one patient of this series developed acute arthritis two weeks after marriage and her husband also developed joint symptoms six weeks later. "L" organisms were cultured from his prostatic secretion. Dienes[41] and his coworkers also reported two female patients, not included in the previous study, who had acute arthritis. The cervical cultures were found to be positive for "L" organisms and negative for gonococci. Venereal transmission was also

suggested by Beveridge, Campbell and Lind[40], who cultured "L" organisms from 3 of 11 women suspected of being the source of nonspecific urethritis occurring in their sexual partners.

It has also been found that "L" organisms exist in the male genitourinary tract and their correlation with arthritis has become better defined. Smith[42] in 1942 was first to isolate "L" organisms from the urethral discharge of a man suffering from urethritis and arthritis. In the following year, Beveridge[43] was able to demonstrate "L" organisms in 4 of 24 men who presented with nonspecific, non-gonococcal urethritis. Harkness and Henderson-Begg[44] were able to isolate "L" organisms in twenty-one (38%) of fifty-seven cases of subacute abacterial urethritis, in five (50%) of acute abacterial urethritis, and in seven (17%) of forty-one cases of Reiter's syndrome. Dienes[41] and co-workers also studied the relationship between "L" organisms and Reiter's syndrome. In 58 of their male patients who had positive cultures for "L" organism, 18 had an acute type of arthritis. Nine of these men presented the entire triad of Reiter's syndrome. In two of these patients with Reiter's syndrome "L" organisms were cultured from the synovial fluid.

Warthin[45] likewise was able to isolate "L" organisms from the urine of two patients with Reiter's syndrome; the same organism was also found in the joint fluid of one of these patients. Wallerstein, Vallee and Turner[46], using a strain of "L" organism have demonstrated significant agglutination titers only in cases which appeared to have Reiter's syndrome. Nevertheless, conclusive proof as to the etiology has not been established. Although a venereal form of the syndrome exists, a certain percentage of patients do not give a history of venereal contact. The problems of pathogenesis and transmission also remain to be clarified.

Clinical Pattern and Course

The syndrome is predominantly limited to the male population. In the postdysenteric form some women have been reported as having the disease. In Paronen's[15] 344 cases, only 34 women were affected. Csonka[23] reported on 185 patients with Reiter's syndrome; 182 were males and 3 were females. Refvem[47] recently added three females cases to the world literature. The entire triad was present in one patient, while vulvovaginitis instead of urethritis was present in the other two patients. This author proposed that vulvovaginitis or cervicitis should be considered one of the cardinal signs in women. Lever and Crawford's[10] second case (which has been questioned) was in a female.

The age of onset has varied slightly in different series. In Csonka's[23] group of patients the age of onset ranged from 15 to 59 years, 82% of attacks having occurred between 20 and 40 years of age. Hollander[11] et al reported on 25 patients whose ages at onset varied from 18 to 37 years and averaged 26 years. In the series Hall and Finegold[18] the median age of their 23 patients was 31 years, with a range of 21 to 41 years. The younger age groups, however, may be affected. Florman and Goldstein[48] reported the syndrome in a four year old boy. The youngest in the literature is Paronen's[15] case of a two and a half year old boy.

Geographic distribution of this syndrome is difficult to evaluate. The early cases were reported from Germany, France, and Scandinavia. This distribution, no doubt, reflected the interest of European physicians in this condition. More recently the majority of cases have been reported in American soldiers who were on duty in the Pacific[49] area. In a larger series of cases, patients came from all branches of the Army and from numerous widely separated camps in the United States, as well as from all major foreign theaters of operations[11]. Specific data as to its frequency amongst different racial groups is limited. Many of the earlier case reports have not included this information. It would appear, however, that there is an increased incidence amongst the white population. In Hall and Finegold's[18] series, all 23 patients were white males. In Csonka's group of 185 cases, 164 were white and 21 were Negro. He likewise noted that the severity of the syndrome was less in his Negro patient. In Montgomery's[50] series

of 38 patients, 36 were white and 2 were Negro.

In most instances the initial symptom is urethritis followed in turn by conjunctivitis and arthritis. About 10% of the patients with the non-epidemic form of Reiter's syndrome may have enteritis as their first symptom[11]. Occasionally conjunctivitis or arthritis may usher in the syndrome. In one case report, glossitis was the first indication of illness[51]. All components may appear within one to four weeks. Fever is frequent at the onset, but in itself is seldom cause for complaint. It is intermittent and usually not high. However, elevations to 103°F. have been reported[18]. The fever is not preceded by or associated with chills and subsides in one to five weeks. Constitutional symptoms vary. Cachexia and debility may be severe, prolonged hospitalization is sometimes necessary. Cutaneous lesions are very frequent and may aid in establishing the diagnosis of the syndrome[52].

The initial attack of the triad may range from two to six months, although the articular component may last as long as one and one-half years[17]. During any single attack there may be exacerbations of the genitourinary, articular or ocular involvement, either separately or in varying combinations. The prognosis for complete recovery of the first attack is excellent. However, recurrences of part or all of the triad within months or years after the initial attack is very frequent. Weinberger and Bauer[21] report a recurrence rate of 75%. Of 185 pa tients, Csonka[23] noted more than one attack in 104 patients. One patient experienced nine separate attacks.

Genitourinary Manifestations

The urethritis may be subacute or acute in nature. The subacute form is characterized by mildness of symptoms and a clear, tenacious urethral discharge. In the subacute form, the discharge may occasionally be mucopurulent, but rarely purulent. Harkness[16] has described the urethroscopic findings. Numerous small wedge-shaped excrescences arise from the mucosal surface and protrude into the urethal lumen. As time progresses, these excrescences become flatter and give the urethral surface a "cobble-stone" appearance[16]. In the acute form of urethritis, the discharge is copious and purulent. It may be accompanied by dysuria, marked frequency, suprapubic pain and even hematuria. Urethroscopy, as reported by Harkness[16], shows a generalized red and inflamed mucous membrane with no excrescences or infiltrations. The urethritis is of variable duration, but usually subsides within two to four weeks.

Genitourinary symptoms are not confined to urethritis. In approximately one-third of the reported patients, an acute exudative hemorrhagic cystitis may be present[21]. On cystoscopic examination these patients show edema of the bladder mucosa, superficial membranous sloughs and diffuse petechial bleeding. Weinberger, Dienes and Bauer[17] observed six patients with acute hemorrhagic cystitis. In one patient the bladder volume was reduced to 75 cc., while in two other patients the bladder wall edema was so marked as to cause obstruction of the ureters. One of these patients developed bilateral hydronephrosis, which necessitated a right nephrectomy and a left nephrostomy. Other authors, likewise, have described this complication. Hall and Finegold[18] have described two patients who have developed bilateral hydronephrosis with dilated kidney pelves and ureters. In one patient there was complete reversal of the hydronephrosis within six weeks.

Colby's[53] second case is of special interest in regard to this type of complication. Following removal of one hydronephrotic kidney because of hematuria, the patient developed a classical picture of Reiter's syndrome. After three months of progressive disease, the normal kidney developed hydronephrosis, which necessitated a nephrostomy. Subsequently, the nephrostomy tube was removed and the kidney assumed a normal appearance. Colby's third case also showed moderate dilitation of both renal pelves and ureters, associated with hematuria. This was observed ten weeks after the onset of Reiter's syndrome and during a phase of marked pyuria. Harkness[16] has even noted dilated renal pelves to be present during the convalscent phase of this illness. Miller and McIntyre[54]

also reported two cases with hematuria associated with lesions of the upper urinary tract, one with pyelitis and the other with dilated left renal pelvis. Besides the above noted complications, prostatitis is very common and prostatic abscesses have been described[53]. Seminal vesiculitis may be another manifestation of genitourinary involvement; however, epididymitis has not been described.

Ocular Manifestations

Conjunctivitis usually follows soon after the onset of urethritis, but may on rare occasions be the presenting complaint. The eye involvement is predominantly bilateral, but Harkness[16] has seen two cases of unilateral conjunctivitis. The severity of the conjunctivitis is highly variable. It may be so slight as not to be noticed by the patient. But in other cases a chemotic conjunctivitis is accompanied by photophobia, epiphora, and a large mucopurulent discharge. Paronen[15] observed conjunctivitis in 239 cases of his series of 334 patients. Hollander[12] noted conjunctivitis in 32 of 53 patients. In the remaining 21 patients the conjunctival involvement was either so trivial as to pass unnoticed, or was entirely absent, even though the disease was typical in every other respect. Cultures of the exudate usually show no growth. The conjunctivitis tends to wax and wane in severity. Hollander[11] et al observed the conjunctivitis to last from two days to three weeks, the average duration being four days.

More serious ocular lesions also can occur in Reiter's syndrome. Vallee[13] noted the development of irititis in his one case. Weinberger, Dienes and Bauer[17] in their 31 patients observed two with episcleritis, four with superficial punctate keratitis, three with iritis, and one with iridocyclitis. Hall and Finegold[18] detected ocular complications in five of their patients. Three patients developed marginal corneal ulcers which promptly healed with little or no residual scar. Two patients had iridocyclitis. It was benign in one, but the other patient had six attacks of iridocyclitis which eventually led to the formation of posterior synechiae. With recurrent attacks of Reiter's syndrome, iritis rather than conjunctivitis may be the only ocular manifestations.

Articular Manifestations

Articular involvement is the most disturbing and persistent feature of the illness. In the initial attack it is usually sudden in onset, and resembles an acute infectious arthritis because of the heat, pain, swelling, and tenderness of the joints. It is nearly always polyarticular with a tendency to establish a migratory pattern. However, monarticular involvement has been described[58]. The larger weight-bearing joints such as the knees and ankles are most frequently affected. Nevertheless, smaller joints, such as the metatarsophalangeal, sternoclavicular, temperomandibular and segments of the cervical spine can be affected. Sweating about the inflamed joints is frequent. Synovial thickening has been described and effusion of the larger joints is not uncommon. Joint involvement may be symetrical, but in more than half of the patients it will be asymetrical[11]. During any single attack the patient may experience remissions and exacerbations of the arthritis. Muscles adjacent to severely involved joints become atrophied and muscular weakness may be marked. This complication is well illustrated in the articles of Sargent[14] and Hall and Finegold[18]. Pain and objective changes may last only a few days in some joints, but in those most severely involved the arthritis usually persists for several months.

The prognosis for complete recovery is usually good, despite the severe polyarticular involvement experienced by many patients. Rarely joint deformity may occur after the first attack. Twiss and Douglas[56] described a patient who during his first attack of Reiter's syndrome developed ankylosis of the proximal interphalangeal joints of the fourth and fifth fingers of the right hand. Roentgenograms showed demineralization of the bones, narrowing of the joint space and actual destructive changes of the proximal phalanges of these fingers. In most instances, however, the roentgenograms rarely show more than a varying degree of demineralization, periarticular thickening and the presence of intra-articular fluid.

With recurrent attacks of this illness, increasing disability with the establishment of chronic arthritis may ensue. Weinberger, Dienes and Bauer[17] have detected chronic arthritic changes in long term follow-up of their patients. Permanent roentgenologic damage was seen in seven of fifteen patients. These changes consisted of narrowing and sclerosis about the sacro-iliac joints in four patients, fusion of one toe, subluxation of a wrist and minor destructive changes in a metacarpophalangeal joint. In the second patient of Guck and Wolf[55], destructive changes occurred in the carpal bones of the left wrist, which subsequently led to ankylosis of this joint. Harkness[16] documents several cases with destructive changes and chronic arthritis. He also has observed laxity of ligaments about joints which has permitted their subluxation. Osteoarthritis superimposed upon previous injured joints has also been observed.

Complete pathological examination of Reiter's syndrome is limited to the investigations carried out by Wepler[57] on a man who died from intercurrent disease. Most studies are limited to biopsy material of joints. Bauer and Engelman[9], in 1942, excised a small amount of synovial tissue from the left knee of a 23 year old man during the thirteenth week of his illness. Gross examination of the knee joint at the time of biopsy showed the synovial lining to be markedly injected but only slightly thickened. In the suprapatellar pouch a few areas were detected which suggested villous formation. Microscopic study showed that the intima of the synovium was several layers deep and contained a moderate excess of lymphocytes, plasma cells and a few leukocytes. There was no evidence of exudate upon the surface. A scant diffuse infiltration of inflammatory cells was present throughout the connective and fatty tissues of the subintimal layer. This layer was hyperemic and slightly edematous. A few perivascular focal collections of lymphocytes and plasma cells were noted in this area. The cellular reaction was that of a mild synovitis. Hyperemia was the most striking feature. Hollander[58] observed at arthrotomy the knee joint of a patient who had the illness for only one week. Although clinically the knee was swollen, warm and painful, the only change observed at operation was slight congestion of the synovial lining. On microscopic examination synovial edema and vascular congestion were present. No abnormal cellular changes or collections were present in this early stage of the disease process.

Another biopsy study of the knee in a different patient at the eighth month of the disease revealed marked changes of the synovium[11]. On arthrotomy the synovia was congested and presented a reddish-purple appearance. No gross thickening of the lining was noted. There were several small circumscribed areas of white fibrinous-like material lying on the synovial surface. Microscopic study showed an intense inflammatory reaction, which was limited to the superficial layers. The synovium was thrown into large club-like projections in which the numerous capillaries were dilated. Each projection was distended by a heavy lymphocytic infiltrate mixed with a few plasma cells and neutrophils. The intima was approximately six to ten layers deep. Perivascular focal collections of plasma cells and lymphocytes were found. In more chronic articular involvement the cartilage is thinned and extensive pannus formation may occur. Under these conditions, the inflammatory process involves the full depth of the synovial membrane[21].

From the above descriptions it can readily be appreciated that the extent and degree of synovial reaction is variable and in itself is of no specific diagnostic value. Although the inflammatory reaction appears to be predominantly limited to the superficial layers of the synovium and therefore distinctly different from the more widespread synovial reaction in rheumatoid arthritis, the type of cellular reaction is not unlike the pathologic picture of rheumatoid arthritis. The synovial response in Reiter's syndrome is proliferative in type but self limited and only in the more chronic forms of the illness is it destructive.

The synovial fluid is similar to that of infectious arthritis and rheumatoid arth-

ritis. It is turbid, clots readily, and is not very viscous. Ropes and Bauer[59] have examined 28 synovial fluids from different patients at various stages of the illness. They found that the average total leukocyte count was 18,890 per cu. mm., with a range from 9,200 to 44,300 leukocytes per cu. mm. The polymorphonuclear cells average 61% of the total leukocyte count. The fluid sugar content was only slightly lower than that of the serum. The mucin content was lowered and average relative viscosity was decreased. Precipitated mucin gave rise to a soft, easily fragmented clot. Synovial fluids from Reiter's syndrome resemble in many respects both those from rheuatoid arthritis and the sterile fluids from gonococcal fluids. Although the fluid may not be diagnostic, it may be of aid in following the course of the illness. Lowering of the leukocyte count, a rise of the mucin and sugar content in serial determinations often indicates subsidence of the inflammatory reaction before it is clinically apparent[21].

Mucocutaneous Manifestations

In recent years, mucocutaneous lesions have assumed greater diagnostic importance in Reiter's syndrome. Balanitis circinata, perimeatal erosions, oral mucous membrane lesions and keratodermia blennorrhagica are the main forms of mucocutaneous involvement. Montgomery[52] et al observed perimeatal erosions and/or balanitis circinata lesions in 30 of their 38 patients. Twenty-three patients had both lesions; four of the remaining seven had perimeatal erosions, while three patients had balanitis circinata alone. In addition, fourteen of these thirty patients (37% of the 38), had painless oral, pharyngeal or glossal mucous membrane lesions. Keratodermia blennorrhagica-like lesions, the keratosis of Reiter's syndrome, occurred in eleven of the thirty patients with mucosal lesions (30% of the 38). Nine presented hard nodular hyperkeratotic lesions, and two had soft parakeratotic patches.

Other authors have observed and reported upon the incidence of mucocutaneous lesions. Hollander[12] noted "balanitis circinata" in 26 and keratoderma blennorrhagica in 6 of 53 cases. Hall and Finegold[18] observed papular lesions upon the prepuce and/or glans penis in 18 of 23 patients. Forty-eight percent of the patients had palate and buccal mucosa lesions. Five patients had dermal lesions morphologically indistinguishable from those of keratoderma blennorrhagica. Cameron[60] saw only two patients exhibiting keratoderma blennorrhagica in a series of 39 patients with Reiter's syndrome.

The balanitis of Reiter's syndrome in the uncircumcised male may appear as small, moist, superficial ulcerations extending from the urethral meatus to the corona. These multiple areas of inflammation, in the beginning, are separated by normal mucous membrane. They then coalesce to form large serpiginous and sharply defined lesions. A soft scaly crust soon covers these patches of inflammation. In the circumcised subject, the lesions have a more hard, hyperkeratotic appearance. The shaft of the penis may also become involved in this process. These lesions occasionally appear early, shortly after the onset of the urethritis, but more frequently come on after the urethritis has completely disappeared. They usually persist for several weeks.

The oral lesions begins as vesicles which soon rupture and leave small, painless superficial ulcers. These ulcers have an erythematous areola and are often coated with a thin, gray-white membrane. These lesions also soon coalesce, forming large, diffuse erythematous patches. They involve the palate, buccal mucosa and tongue. The loss of the papillae of the tongue gives it a "relief map" appearance. A biopsy of the tongue with this lesion was obtained by Abrahamsen[51]. It showed the epithelium to be irregularly thickened with necrosis of portions of the surface. The corium was edematous and contained basophil-degenerated collagen fibers which were infiltrated with lymphocytes and plasma cells. The oral lesions usually appear five to six weeks after the onset of the illness and may last for several weeks.

The more widespread lesion of Reiter's syndrome is a keratotic dermatitis which is identical to keratodermia blennorrhagica. Emile Vidal[61] in 1893 described the lesions in a 24 year old male and

regarded them as a complication of gonococcic arthritis. This contention was held by other authorities for many years, but recently Harkness[62] has challenged this view. In twenty cases of keratodermia blennorrhagica he was unable to isolate the gonocci. He is of the opinion that the skin manifestations are a complication of non-gonococcal urethritis. When these occur in association with gonorrhea, he believes that both infections are present and that the gonococcus plays no part in the appearance of the skin eruption. This conception is gaining wide acceptance.

Keratodermia blennorrhagica in Reiter's syndrom presents two types of lesions, the hard parakeratotic nodules and the soft limpet-like parakeratotic patches. The parakeratotic patches consist of many layers of scales, often heaped up centrally and resembling rupia. The hard parakeratotic nodules are more common and characteristic of the disease. In formation there are distinct phases, the vesicle, pustule and nodule. The lesions are most commonly seen on the soles of the feet and on the lower legs. They start as deep seated vesicles which are soon converted to flat pustules. The pustules become covered by a flat, hard, cornified crust. This eruption may involve other parts of the body. Nails of both feet and hands are frequently involved. Keratotic material begins to heap up under the distal end of the nail plate. The nails become opaque and brittle and the free border broken and roughened. The keratotic material lifts the nail from its base and often causes shedding of the nail.

Biopsy examination of these lesions shows marked acanthosis with elongation and hypertrophy of the rete pegs. There is degeneration of the cells in the prickle cell layer and the infiltration of polymorphonuclear cells and degenerating epithelial cells gives rise to the "spongiform pustular micro-abscesses." The papillary layer of the corium may be infiltrated by lymphocytes, plasma cells and occasionally polymorphonuclear cells. The degree of parakeratosis present varies with the site of the lesion and its duration. Although apparently a specific lesion, keratodermia blennorrhagica both on clinical and histological grounds may be confused with psoriasis. In fact, Auckland[63] believes that keratodermia blennorrhagica is psoriasis.

Cardiac Complications

Cardiac involvement has been noted with increased frequency in Reiter's syndrome. The major abnormalities have consisted of electrocardiographic changes, but clinical findings consistent with myocarditis and pericarditis have also been described. Lever and Crawford's[10] first patient apparently died from a myocardial infarction. Unfortunately, no autopsy was obtained to confirm this clinical impression. Feiring[64] described two cases of Reiter's syndrome in which abnormal prolongations in auriculoventricular conduction appeared. In both cases the roentgenograms of the heart were normal and there were no clinical cardiac abnormalities. Trier's[65] first case demonstrated in the electrocardiogram a prolongation of auriculoventricular conduction time as well as T-wave abnormalities. His second case revealed a marked auriculoventricular conduction defect and sinus bradycardia. In this patient there was slight cardiac enlargement and murmurs were detected. Mayne[66] observed two cases with abnormal electrocardiographic changes not accompanied by clinical cardiovascular abnormalities. Pericarditis was suggested in the electrocardiogram of the first patient; and an electrocardiographic pattern of anterior myocardial infarction was detected in the second patient. Neither electrocardiograms, however, showed a characteristic evolving pattern. Two of the three female patients of Refvem[47] showed abnormal changes as related to the P-R internal, T-waves and S-T segments.

Clinical cardiovascular complications appear to be few. Harkness[16] has observed, in two cases, tachycardia with pulse rates which varied between 120 and 150 over periods of five to six weeks. Warthin's[45] first case presented evidence suggestive of acute myocarditis. The electrocardiogram showed a markedly prolonged P-R interval, with second degree heart block and inverted T-waves in lead II. The heart sounds were of a poor quality and the pulse was sugges-

tively dicrotic in character. Pericarditis has been described by Csonka and Oates[67] in two cases. A pericardial friction rub was detected in both patients. In the first case the electrocardiogram did not show the characteristic evolution of pericarditis. It was abnormal because of prolonged P-R interval and minor S-T segment elevations. The second patient did not have a characteristic Reiter's syndrome, but rather an acute abacterial urinary infection following sexual exposure. The electrocardiographic changes supported the clinical impression of pericarditis.

Laboratory Findings

During the acute and active stages of the illness the sedimentation rate is elevated, the C reactive protein test is positive and a mild to moderate leukocytosis is present. The sedimentation may not reach its peak until about five to six weeks after the onset of the arthritis and may remain elevated for weeks to a few months after the patient has been clinically asymptomatic. Urinalysis may show traces of albumin. Microscopic examination of the urinary sediment may show clumps of pus cells, occasional red blood cells and rarely casts. The findings are dependent on the stage of the illness and the severity of the genitourinary involvement. In severe cases a secondary hypochromic anemia may be seen.

Serum uric acid, non-protein nitrogen and blood protein determinations are normal. Refvem[47], however, detected an elevated serum alpha$_2$-globulin in two cases. Hall and Finegold[18] performed a battery of liver function tests in six patients and showed an abnormal cephalin cholesterol flocculation in three. In one of their patients having involvement of the upper thoracic vertebral articulations, the spinal fluid revealed no pleocytosis but the protein concentration was 92 mg. per 100 ml.

Agglutination reactions of serum of patients having Reiter's syndrome against various organisms has not been of diagnostic help. Storm-Mathisen[68] reported a diagnostic skin test. The test material was a mixture of joint exudate and lymph node emulsion obtained from a patient with Reiter's syndrome. On intradermal inoculation, five patients suffering from Reiter's syndrome developed a red papule within forty-eight hours after testing. Eleven patients, serving as controls, developed no papule on inoculation. To my knowledge, this interesting and provocative experiment has not been repeated.

Treatment

In Reiter's syndrome, the effectiveness of any form of therapy is difficult to evaluate. The disease process is self-limited and characterized by a variable duration. As in any disease of unknown etiology, supportive measures, both local and general, are of major importance. The urethritis in the average case, unless complicated by gonorrhea, can best be treated with tincture of time. The anxiety which accompanies this phase of the illness may well be the major problem. We have found that simple conversation and reassurance is more effective than urethral irrigations, dilatations, and soundings. The conjunctivitis may be controlled by compresses or bland irrigations of mildly antiseptic solutions.

Arthritis is the most challenging aspect of Reiter's syndrome. Sodium salicylates in analgesic doses are helpful in controlling joint pain, but appear to have no influence upon the course or duration of the illness. Fowler and Knight[69] question the effectiveness of any drug or combination of drugs to alter the course of Reiter's syndrome. On theoretical grounds, streptomycin and terramycin have been advocated by certain workers, but the small number of cases so treated makes evaluation of their worth difficult[45, 58]. Fever therapy, in its various forms, has also had its claimants[14, 70, 71].

In recent years, ACTH and cortisone have entered the therapeutic parade. Ogryzlo and Graham[72] reported dramatic improvement in three patients with Reiter's syndrome who received adrenocorticotropin therapy. Symptoms returned in all three within a few hours to two days after treatment was discontinued. Goldeck and Donat[73] also reported marked improvement of one patient treated with adrenocortropin after failure of fever therapy, Aureomycin, gold and bismuth therapy. In 1953 Larson and Zoeckler[74] reported on four patients who

were treated with ACTH. These patients improved under therapy, but soon relapsed after ACTH was discontinued. The authors consider that ACTH as an adjuvant has a definite place in the management of Reiter's syndrome. Foxworthy[75] et al used ACTH and cortisone in ten patients with severe Reiter's syndrome. In their experience ACTH and cortisone, when given in adequate doses for a long enough period of time, were effective in suppressing symptoms. The course of the disease, however, was not shortened by therapy. While not curative, ACTH and cortisone, have become the most valuable agents now available to control the symptoms of patients with severe Reiter's syndrome.

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DISORDERS OF INTESTINAL ABSORPTION

I. The Primary Malabsorptive Syndromes: Current Concepts and Problems

JEROME M. SWARTS, M.D.*

It is the purpose of this presentation to review currently available information, current concepts, and problems that have to do with the nature of the primary malabsorptive syndromes.

The term, malabsorption or malabsorptive syndrome(s) is in many respects more meaningful than some of the older ones, but has the disadvantage of being generic, and hence applicable to numerous clinical states. Sprue is a word of Dutch origin (sprouw); its use in modern times being accredited to van der Burg in Java and to Manson in China in the latter part of the last century. Holst, a Dutch physician, first employed the term, nontropical sprue in 1927. Gee in England in 1888 and Herter in this country twenty years later described the malabsorptive syndrome of children known as celiac disease[1].

It is convenient to think of the malabsorptive syndromes as being primary or secondary. Celiac disease, nontropical sprue and tropical sprue fall into the former category. In the latter group are a variety of organic diseases and surgically induced defects of the alimentary tract causing impaired absorption. The secondary malabsorptive syndromes will not be considered in detail in this paper.

Excellent descriptions of the clinical manifestations of the primary malabsorptive syndromes are readily available[2,3].

The Nature of the Absorptive Defects

Steatorrhea was first observed in this group of disorders probably because its effect upon the feces is usually obvious. Steatorrhea may reach very high levels and the proportion of ingested fat which is absorbed may be extremely low. In a recent study[4], maximal fecal fat excretion with a moderate fat intake was 67 grams per 24 hours; with a low fat intake, the proportion of ingested fat excreted was 88%. Fecal losses of fat (and nitrogen) increase with increasing intake, but percentage absorption is greater. At lower levels of intake, percentage absorption is less but fecal losses are smaller.

The association of grossly normal stools with normal frequency of defecation and marked degrees of steatorrhea has been noted and deserves emphasis[2,5,6,7]. In Cooke's series of patients 20% were without diarrhea in the presence of fecal fat values as high as 27 grams; in another group of patients fecal fat values as high as 49 grams per 24 hours were associated with normal bowel function[6]. Patients may present with tetany[7], osteomalacia[6,7] or anemia[5] in the presence of grossly normal stools.

Seventy to 80% of fecal fat is present as fatty acid or soap with about one-half of the split fats consisting of soaps, although this may vary considerably[8]. According to Frazer[9], most of the fatty acids belong to the saturated series in moderately ill patients. Weijers and van de Kamer[10] have demonstrated an increase of unsaturated fatty acids in very severe disease.

Numerous studies in recent years have shown that the absorptive abnormality is not limited to fat[4,11,12].

Protein loss is often excessive, as indicated by elevated fecal nitrogen values. In one study the fecal nitrogen loss reached 50% of intake with relatively low levels of dietary nitrogen[4]. The caloric deficit in this study, based upon fat and nitrogen loss, averaged 427 and reached a maximum of 728 per day. Defective urea[13] and glycine[14] absorption reflect malabsorption of materials of this class. It is of interest that the greater the defect in fat absorption, the more marked are the abnormalities of nitrogen and mineral absorption[4,12].

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TABLE I.

MALABSORPTIVE SYNDROMES

I. Primary malabsorptive syndromes

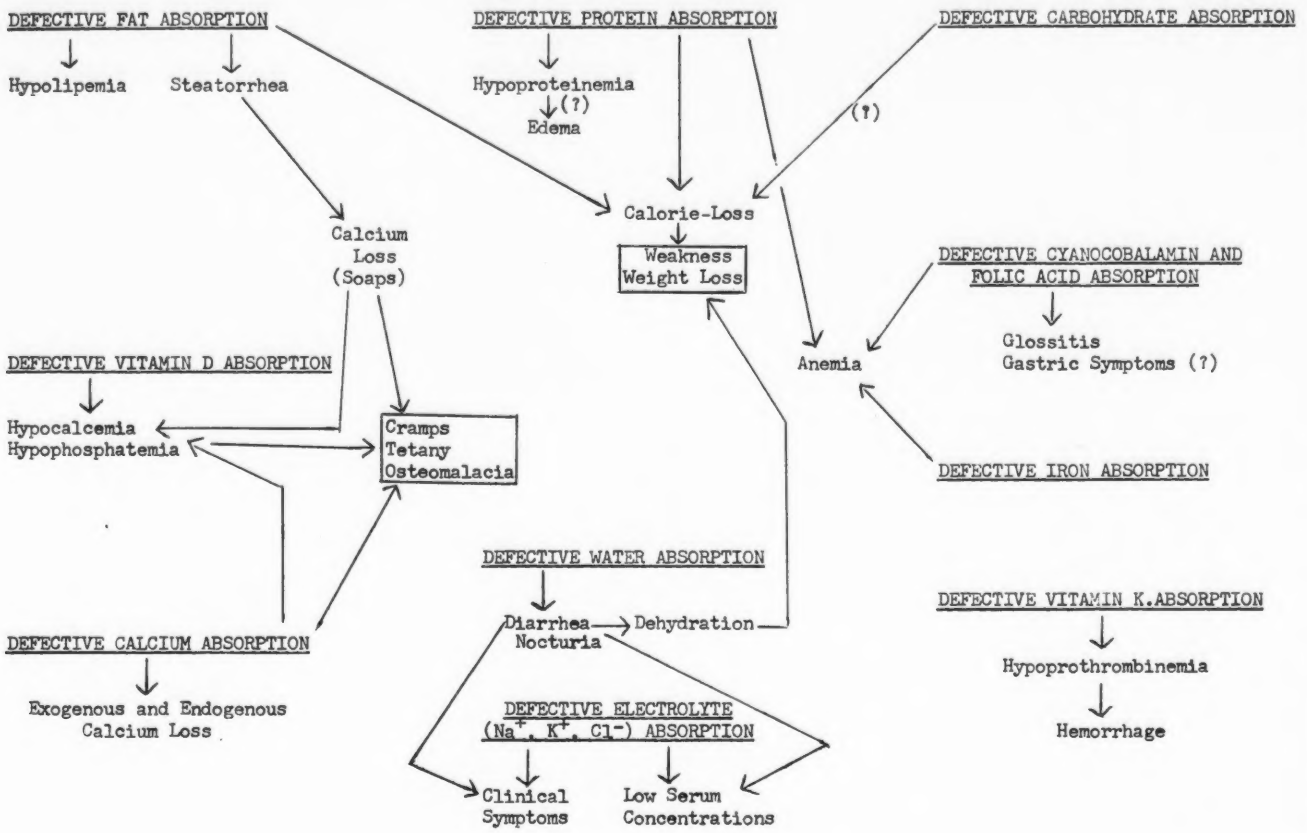
- A. Celiac disease
- B. Nontropical sprue
- C. Tropical sprue

II. Secondary malabsorptive syndromes

- A. Small intestinal diseases
  1. Regional ileitis and ileojejunitis; enterocolitis
  2. Tuberculous enteritis
  3. Lymphoma
  4. Whipple's disease
  5. Scleroderma
  6. Amyloidosis
  7. Massive diverticulosis
  8. Gastrojejunocolic fistula
- B. Surgically induced
  1. Gastric resection: total and subtotal
  2. Small bowel resection
  3. Strictures and anastomoses
  4. Gastroileostomy
  5. Pancreatectomy
- C. Hepatic disease
  1. Hepatocellular defect
  2. Intrahepatic obstruction
- D. Extrahepatic Biliary disease
  1. Obstruction
  2. Biliary fistula
- E. Pancreatic diseases
  1. Chronic pancreatitis
  2. Neoplasm
  3. Mucoviscidosis (cystic fibrosis)

Carbohydrate absorption, as measured by oral glucose tolerance tests[13,15] and by intestinal intubation[16] studies of absorption and tolerance, is impaired. Defective absorption of xylose[17], rhamnose[18] and fructose[19] has also been demonstrated.

The hemorrhagic tendency, known for many years, was elucidated by Kark in 1940[20], when he established that the spontaneous bleeding and abnormal coagulation were related to hypoprothrombinemia which could be readily corrected by parenteral administration of vitamin


DEFECTIVE FAT ABSORPTION
Hypolipemia
Steatorrhea
DEFECTIVE PROTEIN ABSORPTION
Hypoproteinemia
(?)
Edema
DEFECTIVE CARBOHYDRATE ABSORPTION
(?)
Calorie-Loss
Weakness
Weight Loss
Calcium
Loss
(Soaps)
DEFECTIVE CYANOCOBALAMIN AND
FOLIC ACID ABSORPTION
Glossitis
Gastric Symptoms (?)
Anemia
DEFECTIVE VITAMIN D ABSORPTION
Hypocalcemia
Hypophosphatemia
Cramps
Tetany
Osteomalacia
DEFECTIVE IRON ABSORPTION
DEFECTIVE WATER ABSORPTION
Diarrhea
Nocturia
Dehydration
DEFECTIVE VITAMIN K.ABSORPTION
Hypoprothrombinemia
Hemorrhage
DEFECTIVE CALCIUM ABSORPTION
Exogenous and Endogenous
Calcium Loss
DEFECTIVE ELECTROLYTE
(Na+, K+, Cl-) ABSORPTION
Clinical
Symptoms
Low Serum
Concentrations

K. This aspect has been reviewed in detail recently by Wang and Bossak[21].

Fourman and Spray[22] have demonstrated that ordinary doses of vitamin D given orally, with or without restriction of dietary fat, do not improve calcium absorption. Very large doses of the vitamin are necessary to elicit a response, the degree of which is not predictable; however, ordinary doses of vitamin D given parenterally produce an excellent response in terms of calcium retention.

The rate of vitamin A absorption is reduced in sprue[23,24]. Flat blood curves are obtained with both oily and water-miscible preparations, and excessive fecal excretion of the vitamin occurs irrespective of which preparation is used.[24].

Impairment of calcium absorption produces hypocalcemia, osteomalacia and tetany. The customary explanations invoked to explain this abnormality have been: (1) precipitation of calcium by fatty acids in the gut and (2) impaired absorption of vitamin D. Several observations are pertinent in this regard. Badenboch and Fourman[25] presented evidence that the osteomalacia of steatorrhea is due in part to failure of vitamin D absorption, in part to calcium in the gut combining with unabsorbed fat, and finally to a defect in calcium absorption *per se*. Calcium absorption is not significantly improved by a fat-free diet[4]. Metabolic studies employing radioactive calcium[26] indicate that the excessive loss of calcium in the feces is due to increase of digestive juice volume, poor reabsorption of digestive juice calcium and poor absorption of dietary calcium. In severe cases fecal calcium may be higher than calcium intake. Fecal phosphorus levels are also high and may exceed the percentage lost in the urine[4].

Excessive losses of potassium in the feces often leading to hypokalemia have been reported[4]. Large fecal losses may occur in the presence of stools of normal consistency. Potassium loss appears to be independent of diarrhea but is of course greater when this symptom exists, and may reach levels as high as two grams per day[12].

Large fecal losses of sodium and chloride are common[4,12]. Studies employing radiosodium implicate a defect in both the nontropical and tropical varieties of sprue[27].

The observation that there is delayed excretion of water and nocturnal diuresis in sprue[28] has been confirmed by Taylor[29] who showed that this phenomenon occurred in fasting as well as in nonfasting patients and is therefore not a secondary effect. This then has been interpreted as a primary absorptive defect rather than a secondary, compensatory mechanism, as originally supposed.

Iron absorption has received scanty attention until recently. Radioactive iron studies have shown defective absorption in sprue[30]. It seems reasonable to suppose that deficient nitrogen absorption, deficient cyanocobalamin absorption and iron deficiency contribute to the anemia and account for the variations found in these disorders.

Studies utilizing isotopic labelled vitamin B_{12} (cyanocobalamin) have shown that there is marked impairment of the ability of the small intestine to absorb this substance and that the feeding of intrinsic factor does not enhance cyanocobalamin absorption[31,32,33]. This absorptive defect is also reflected in low serum levels of cyanocobalamin[34].

The frequent association of megaloblastic anemia with malabsorptive states has also suggested the possibility of folic acid deficiency. Recent studies by Girdwood[35] and by Butterworth and co-workers[36] have provided objective evidence of folic acid deficiency. Butterworth's studies, however, suggest that this is neither a permanent nor a specific defect.

The large fecal losses of fat, nitrogen and electrolytes explain the hypolipemia, hypoproteinemia, hypocalcemia, hypophosphatemia, hypokalemia and hyponatremia found in the study of patients with malabsorptive syndromes.

The major absorptive defects and their consequences are depicted in Figure 1.

Diagnostic Tests of Absorptive Function

Diagnostic tests which have been employed in the study of primary disorders of absorption are chiefly: (1) those related to fat absorption, (2) those related to protein absorption, (3) those related to absorption of certain of the vitamins,

(4) those related to carbohydrate absorption and (5) those having to do with water absorption.

On the basis of intake-excretion (balance) studies, fecal fat excretion will vary somewhat with intake in normal subjects. At a level of intake of 100 grams of fat the fecal excretion should not exceed 4.6 grams in 24 hours[37]. Expressed as percent-absorption ("coefficient of absorption") a value of over 90% may be acceptable[38], but the unequivocally normal range is between 96 and 99% of intake[8]. Abnormalities of fat absorption are best expressed as amount excreted rather than as percentage-absorption. Expressions relating fecal fat to fecal weight are meaningless and should be discarded. When isotopic labelled fat (I^{131}-triolein) is employed, mean urinary radioactivity is 55% of the ingested dose[39] and fecal radioactivity is 4% or less of the ingested dose[40].

Blood curves following the oral administration of fat (e.g., butter) show a flat type of curve (serum turbidity)[41,42]. Plasma radioactivity curves are also flat following administration of labelled fat[39]. Blood curves are of limited value and have been criticized because they represent rate of absorption rather than total quantity absorbed; in the case of labelled fat the criticism has been offered that the measurement is that of blood radioactivity rather than of blood lipids[43].

Fecal nitrogen excretion has also been used as a test of malabsorption and often discloses evidence of abnormal nitrogen loss[4,11,12]. Labelled protein has been used in the study of secondary malabsorptive states[44,45] but no published reports of studies in patients with sprue are available.

Labelled cyanocobalamin (Co^{60}— or Co^{58}—B^{12}) has been used in several studies, employing measurement of hepatic uptake[31], urinary excretion[33] or fecal excretion[32]. The test is simple and contributory.

Girdwood has suggested the use of the differential urinary folic acid excretion test as a valuable procedure but technical difficulties have limited its acceptance[35].

Since Thuysen suggested the use of the flat oral glucose tolerance curve as a criterion for diagnosis, this test has been widely employed. Several recent studies have confirmed its usefulness[13,15,46]; others, however, have questioned its value[47].

Xylose, which is absorbed without phosphorylation and which is not metabolized, has been employed by Fourman[17] and more recently by Gardner and Perez-Santiago[41] and by Benson et al.[48] who have confirmed its usefulness and simplicity. The urinary xylose excretion test appears to be a reliable means of measuring carbohydrate-malabsorption.

Vitamin A tolerance curves have been employed in the study of patients with malabsorptive syndromes[23,24,41]. Flat curves have been obtained frequently. The test presents certain technical difficulties, is affected by hepatic dysfunction and is an index of the rate of absorption rather than of the quantity of absorption. Recently Wenger and others[49] have employed the measurement of fasting blood carotene levels as a diagnostic aid in screening patients. Liver disease, fever and nutritional deficiency also result in low levels.

Wollaeger and Scribner demonstrated delayed excretion of water in sprue[28]. This observation was later confirmed by Taylor who suggested the use of the water-loading test in excluding patients with non-steatorrheal diarrhea[50]. The test may be misleading since it is positive in the presence of renal disease, heart failure, adrenal insufficiency, ascites, severe iron deficiency anemia and pernicious anemia. It is a simple, inexpensive screening test.

Other tests of absorption which have had limited acceptance are the chylomicron count performed after a fat meal[38,42] and the Lipiodol test[51]. Microscopic examination of feces for the presence of excessive fatty acid crystals in stool is not a reliable method of detecting fat malabsorption[8].

Etiologic Considerations

Anatomic Changes

For many years it has been considered that the morphologic alterations in the small intestine of sprue were of no etiologic significance and represented secondary changes. Butterworth and Perez-

Santiago have reported antemortem changes in the small intestine in tropical sprue, consisting of edema, inflammation and widening of the villi[52]. Adlersberg and Schein reported changes in autopsied patients but these were varied and inconstant[53]. Shiner has presented biopsy material in sprue patients which indicates that mucosal atrophy is a feature of the disease[54]. Cytologic examination of exfoliated gastric cells in tropical sprue has disclosed abnormalities similar to those associated with pernicious anemia[55]. None of these observations answers the question as to the significance of the structural alterations.

Motor Function of the Intestine

Abnormal motility patterns are seen frequently in patients with primary malabsorptive disorders[56,57,58]. These consist principally of dilatation of the jejunum, and segmentation and scattering of the barium column through the small intestine; transit time may be delayed or normal. Ingelfinger and Moss, by means of intraluminal pressure studies, demonstrated hypomotility and hypotonicity of the jejunum in sprue and were able to augment motility by means of mecholyl[59]. May *et al.* produced simultaneous augmentation of motility and improved absorption of glucose by mecholyl stimulation in children with celiac disease[60]. Similar observations have been made by Cummins and Almy in patients with nontropical sprue[61]. A recent observation concerning the relationship between motility and absorption is that the administration of an anticholinergic drug, methantheline, inhibits motility and produces significant reduction in the rate of absorption of D_2O and radiosodium from the small intestines of healthy persons; the authors attributed the effect to a diminution of the absorbing surface area as a consequence of the hypomotility caused by the drug[62].

Intestinal Secretion

Radiographic[56,57,58,63] and duodenal intubation[64] studies suggest that mucus secretion in the small intestine is increased. Flocculation of aqueous suspensions of barium sulfate has been noted repeatedly. The use of a nonflocculating suspension eliminates the abnormal mucosal pattern, but motor abnormalities are unchanged[63].

Smart and Daley have studied intestinal "mucus" grossly and microscopically in tropical sprue[64]. In contrast to the intestinal secretion of normal subjects, the intestinal contents appears as clumps and threads containing fat droplets which are irregularly dispersed. They suggested that failure of digestion of mucus results in interference with absorption of fatty acids and that this defect might well be due to lack of the mucus-splitting ferment.

Reversibility of Tropical Sprue

Frazer[66] maintained that there was no relationship between folic acid and fat absorption. Careful studies by several groups of workers[41,65,67,68] have substantiated this concept thus lending weight to the point of view that tropical sprue is not a reversible nutritional deficiency. Black and Fourman have demonstrated rapid clinical improvement but without change in fat absorption following the use of liver extract or folic acid[38]. Studies of folic acid, B_{12} and liver extract in the treatment of tropical sprue suffer from several inadequacies: (1) poor follow-up observations, (2) no absorption studies or questionably valid ones, and (3) the use of special diets while the therapeutic agents under investigation were being administered.

In regard to the relationship of nutritional deficiency to malabsorption, it has been pointed out that sprue is not seen under conditions of dietary deficiency in certain parts of the tropics, e.g., Africa, where other diseases due to dietary deficiency are common; that extreme starvation in Japanese prisoner-of-war camps did not lead to it; and finally, that sprue has been observed in patients taking an excellent diet[69].

Genetic Transmissibility

That these may be genetically transmissible disorders has received some attention in recent years. Cooke et al. in a study of 100 patients with nontropical sprue found ten families in whom the presence of steatorrhea was confirmed in more than one member; in five additional families the existence of familial incidence was strongly suggested[2]. Davidson and Fountain found this to be true

for idiopathic steatorrhea (nontropical sprue) and celiac disease[70]. Thompson has presented evidence that there is a genetic susceptibility to celiac disease and that late maternal age and late birth rank favor development of this susceptibility[71]. Among 150 patients with tropical sprue, 75% gave a family history of sprue or pernicious anemia[72].

The Relationship Between Celiac Disease and Nontropical Sprue

The relationship between celiac disease and nontropical sprue has been receiving considerable attention. Forty-three per cent of Cooke's patients with nontropical sprue gave a history of onset of symptoms in childhood[2]. In another study[70] this figure was 34%. A follow-up study of patients with celiac disease, five or more years after onset or diagnonsis, revealed no complete recoveries[73].

Implications of the Therapeutic Response

Dicke, Weijers and van de Kamer observed that children with celiac disease improved when wheat and rye flour were excluded from their diets[74]. They demonstrated that there was a decrease in fecal fat under these conditions and that introduction of wheat flour, but not wheat starch, led to deterioration. Anderson *et al.* studied ten children with celiac disease and found striking clinical improvements on a wheat-free die which was accompanied by parallel increase in fat absorption, improved absorption of glucose and improved radiographic appearance of the small intestine[75]. Schwartz and others in this country have studied adult patients in great detail[11]. These workers found that on a gluten-free diet, there was a reduction in the fecal losses of nitrogen, fat, sodium, potassium, phosphorus, magnesium and calcium, which paralleled clinical remission. In another study of patients with nontropical sprue, the exclusion of gluten corrected the absorptive defects with the exception of that which resulted in iron deficiency[76]. The reversibility of glucose malabsorption was variable in the last two studies. In an extensive study of twenty-two patients with nontropical sprue, six failed to recover[77]. The authors concluded that on the basis of therapeutic response, the illness is etiologically analagous to celiac disease since the same sequence of events occurs in both. In children the recovery period is 3-6 weeks, while in adults this is often 3-6 months. Of interest is the observation that three cases of tropical sprue did not respond to the withdrawal of gluten[77].

Wheat and rye flour which both cause deterioration in celiac disease also make dough suitable for bread-making; maize and rice, although containing gluten, can be given in any quantity to celiac children without causing deterioration. The dough-making properties depend ultimately upon the chemical constitution of gluten. An antigenic relationship has been demonstrated between wheat and rye gluten (and also barley) by the induction of allergic and immunologic phenomena in guinea pigs; more significantly this cross relationship does not extend to maize-gluten. It is suggested that the soluble breakdown products of wheat and rye gluten cause a tissue reaction of an allergic nature in the small intestine resulting in an increased secretion of mucus which delays absorption. Failure to respond to such a regimen may indicate that some other disease may be responsible for failure of absorption (and justifies laparotomy as a diagnostic procedure)[77].

The favorable effect of cortisone and ACTH on the clinical state and absorptive defects in nontropical sprue is now well known. Reversibility of the absorptive defects is much less complete with this mode of therapy and improvement is not maintained when drugs are withdrawn or reduced below a given therapeutic dose[78,79,80]. Schwartz *et al.* have suggested that the efficacy of this therapy lies in the interference with the intestinal reaction to gluten[11].

A final word about recent therapeutic efforts and their implications is in order. French *et al.* reported unequivocally beneficial, clinical and absorptive responses in a group of patients with tropical sprue treated with one or more courses of sulfonamides and antibiotics. The therapeutic benefits were sustained for two to four years. The authors assumed that the effects were due to the

antibacterial action on the intestinal flora[69].

Some Unsolved Problems

The accumulation of observations and the introduction of new techniques have eliminated numerous misconceptions of the past, but many interrelationships and conflicting observations need to be clarified and reconciled. With a greater understanding of these absorptive disorders, new avenues of investigation have been opened.

The relationship between tropical and nontropical sprue is far from clear. The genetic aspects of both tropical and nontropical varieties require further investigation. The mechanism by which wheat and rye gluten produce malabsorption in susceptible individuals requires elucidation. The possibility that other constituents of the diet may have a similar effect in certain individuals merits exploration. The manner in which pituitary corticotropin and cortisone produce beneficial effects has never been explained. The role of intestinal hypersecretion and that of disordered intestinal motor function deserve further study. Are these causative mechanisms or secondary manifestations? The possibility of bacterial interference with absorption, especially in tropical sprue, has not been settled. The morphologic changes in the intestine can also be interpreted as being etiologically significant or as secondary effects. Finally the hypothesis of an enzymatic defect at the level of the intestinal cell deserves further study. These are but a few of the unsolved problems related to the primary malabsorptive disorders.

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THREE DIMENSIONAL VASCULAR ILLUSTRATION TECHNIQUE*

LEON H. STRONG, Ph.D.**

In the study of blood vessel development of mammalian embryos, the capillaries are so small, and plexus formation so prevalent that accurate illustration of them has always posed a problem. In the early literature, descriptions were made often from a single embryo, some even from a few sections of one. Thus, nothing like the living condition was ever presented. By and large, during the last quarter of this century, morphological study among vascular embryologists has had few investigators. Thus, it is true that the latest editions of embryological textbooks still perpetuate generalizations based upon early erroneous work. Adequate study may be made, only, when large numbers of embryos are investigated. Anomalies may be avoided by doing so, and thus an average condition may be presented.

In certain vascular studies, long distances of different systems of anastomosing vessels must be traced and correctly connected. This cannot be done with ease or at all by the wax reconstruction method. Even if capillaries have received an injection of an opaque substance many vessels have failed to fill.

Reconstructions made from thin sections have been of little aid in depicting such capillaries. A major difficulty has been to show collapsed vessels and particularly collapsed networks. The ordinary injection methods have two faults. First, trauma causes constriction of vessels which will not fill if the specimen be alive, and second, pressure from the injecting apparatus overly distends the vessels or causes extravasation if the animal be dead.

The usual manner of injection is done upon dead embryos recently removed from, or after they have been removed from the mother for some time. Failure to inject the entire embryo has been the common result.

We have devised a method which, functionally follows the normal course of blood flow in the living embryo. Our method, therefore, gives a normal living picture of the capillaries. It is important to recall that skin vessels are easily injectable by many methods but that deep vessels may not take injection at the same time. When injection fails an investigator loses time and valuable material for he must be able to make a selection of embryos showing the entire capillary bed if his results are to go unquestioned.

We have found Higgins' Eternal India ink to be an ideal injectant. This fluid is close to a solution of colloidal carbon. It passes through the smallest capillaries with ease. This India ink is tolerated sufficiently well by both the blood stream and the endothelium of the living embryo so that a complete injection of all capillaries is accomplished.

Method of Preparation

Under ether anesthesia we remove the embryos one by one from the mother. We place them in water at blood temperature (saline may be used, but is unnecessary after the technique is well practiced). Then we cut their membranes, cannulate the umbilical vein with a glass cannula, cut the umbilical artery, and carefully introduce various concentrations of India ink, by means of breath pressure through a saliva trap connected to the cannula by a length of rubber tubing. The ink travels as in the living to the heart. It is propelled by the heart throughout the vessels and capillaries of the embryo, filling them completely. The embryos, after injection, are immediately dropped into formalin where they remain over night, or if longer than 20 mm for a period of 24 hours. They are then washed in water for 24 hours then in distilled water, and in turn run through changes of alcohol to dehydrate them thoroughly. They are transferred to xylene, then to benzol, and finally to benzylbenzoate. In

*Photography by Tom Scanlan.

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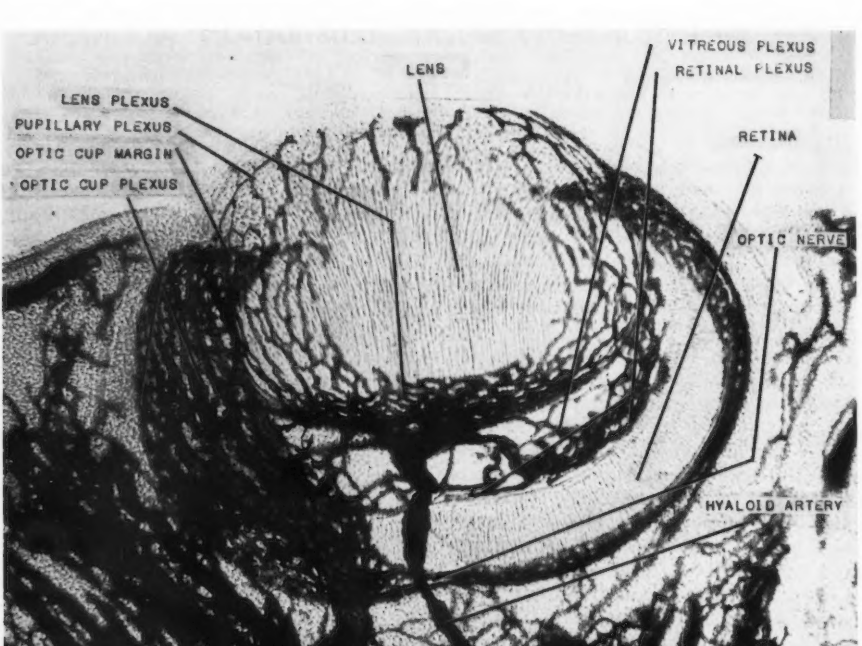

the latter the tissues of the embryos become crystal clear. Thus, the ink in the vessels stands out in silhouette. The embryos may be elevated on blocks of thick glass and inspected with a dissecting stereomicroscope. They may be dissected in benzylbenzoate, or selected for mounting as a whole or for sectioning.

Since certain tissues have slightly different refractive indices or present curved surfaces, the outlines of such structures may be made out. Methylene blue and certain stains not soluble in oil may be used to bring out tissues.

We have found that either whole embryos or thick sections of from 100 to 500 mu are ideal for study under the stereomicroscope. Thick sections permit a macroview of a microfield—an overall picture of a microscopic region. This cannot be had by the solid reconstruction method and is much to be preferred to other transparent methods for precision of relationships. The material, since it is crystal clear, may be photographed, with the result that much of the three dimensional effect is preserved. Large photographs (8x10 or larger) may be made. Thus, microstudy is put on a macrobasis. This saves time. Minute points, only, need checking on the original material.

In order to produce a specimen which will show its vessels to advantage, it is necessary to make it as transparent as possible. It is an advantage to have it free from discoloration if photography is to be used. Of modern clearing agents, methylsalicilate (oil of wintergreen) has been extensively used. This however discolors the specimen in a rather short time. We have found that benzylbenzoate is by far the ideal clearer; our more than 20 year old specimens are still crystal clear. To continue the transparency of the specimen to its final state, we have found that twice filtered but carefully selected boules of gum dammar in zylene

(Continued on page 77)

SOME RECOMMENDATIONS REGARDING COMMON FRACTURES IN CHILDREN

DONALD S. MILLER, M.D., Ph.D.*

The types of accidents that occur in children are no longer so different from those in adults, except for accidents to the industrial worker, as they were in the days before the automobile and the motor scooter. Regarding the long-term and sometimes the immediate effect of the accident and the approach to treatment of fractures, it does make some difference whether the patient is a child or an adult. Although fractures resulting from motor vehicle accidents are as varied in children as in adults, in children, they are likely to be associated with greater injury to the soft tissues and accompanied by injuries to bodily systems other than the skeletal system. Fractures incurred at play and by falling during normal activities of childhood are likely to be clearcut and simple rather than compound. Fractures through roller skating accidents or even ice skating are not so prevalent as formerly. When they happen, the fractures are ordinarily of the Colles or wrist type, of the clavicle, and of the ankle.

Some Types of Fractures and What To Do About Them

Fractures of the Wrist and Forearm.

A high percentage of all fractures in children occur in the bones of the wrist and forearm. Such fractures may be of the simple cortical or greenstick type without angulation, or they may be seriously displaced, overriding and angulated. The upper third, middle or lower third of the shaft may be affected, although the distal part is injured most. Fractures in the upper third, middle or lower thirds of the forearm do not, as in adults, require precise anatomic positioning of the fragments in supination, midpronation-supination or pronation; nevertheless, when the fracture is in the upper third of the forearm, the fragments must be supinated slightly more than when the fracture is in the middle third of the forearm. Similarly, fractures in the lower third must be pronated more than those in the middle third. The surgeon should observe the direction of pull and strain in and around the fractured sites, observe the way of the muscles during pulling. Awareness of muscle dynamics assists surgical judgment regarding the degree and direction of anatomic positioning.

Two serious fractures in this area require special attention: The first is a fracture of the lower sixth of the bones of the forearm with dorsal displacement of the distal short fragments. The second is the Monteggia fracture or fracture in the upper sixth portion of the ulna and dislocation at the head of the radius. The first calls for reduction of the fragments by hyperextension and traction. The surgeon's thumb serves as a lever in bringing the fragment over the fractured site. The patient's forearm is placed in pronation before a properly fitting light-weight cast is applied.

The Monteggia fracture calls for careful reduction and alignment without displacement, angulation or shortening of the ulnar fragments. The head of the radius must be returned to the radiohumeral site. One seldom opens the elbow joint for replacement of this bone. A Monteggia fracture in adults is usually disastrous. Ordinarily the results of treatment for children is satisfactory, although complications of the neurovascular-muscular systems are possibilities brought about by tight casts which cause compression of the hemorrhagic or edematous area in the flexor muscles. This may lead to the serious consequence of Volkman's ischemic contracture. Occa-

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sionally a spicule of bone cuts into an artery, causing either a false dissecting aneurysm or an arteriovenous aneurysm. Two such serious instances have come to my attention in which the brachial artery and vein were penetrated near the elbow joint.

Treatment of the simple cortical fracture without displacement is by soft-material immobilization or the application of a light-weight cast. This reduces the swelling and relieves pain. An arbitrary figure of about 20 per cent may be used as the angle for reduction in correcting the fractured site by manipulation with or without general anesthesia. Angulation at the middle third of long bones takes longer to correct and may eventuate in some permanent angulation. The site of a fracture in and about an actively growing epiphysis reforms and corrects itself satisfactorily if left undisturbed. When a general anesthesia and manipulative correction are indicated, alignment must be carefully accomplished so as to prevent angulation and rotation. Roentgenograms should be taken immediately after reduction and again within a seven to fourteen day period. This is necessary because sometimes after edema subsides the fragments slip and deformity results unless corrective manipulation is repeated.

A molded cast, adequately padded, should be applied as a rule from the axilla to the knuckle line of the hand. The period of immobilization varies from four to six weeks in the age group from 2 to 6 years, somewhat longer during adolescence.

Roentgenographic examination is again necessary immediately upon removal of the cast so as to ascertain the amount of new callus and whether alignment and union are satisfactory.

In general, children do not require physical therapy. They recuperate rapidly, and their return to normal activity provides sufficient stimulation for healing and restoring function to the joints.

Fractures of the Elbow Joint. Fractures of the elbow joint at the supracondylar level are frequent. The extent and severity of fractures in this area vary from small infractions and cracks without displacement to extremely displaced fragments with intra-articular hemorrhages. Deformity and pseudoparalysis are not infrequently consequent problems.

Roentgenologic studies obviously are essential before attempted reduction. In most cases reduction may be accomplished in complete flexion under general anesthesia. Forced flexion is not necessary. By hyperextension of the fractured fragment and gentle traction, the distal fragment can be brought into direct alignment with the larger proximal portion of the humerus. A well padded circular cast is worn for four to six weeks; a sling is also worn throughout this interval and continued to be worn while a secondary soft tissue bandage replaces the cast.

When initial swelling interferes with the procedure for reduction just described, traction may be applied by one or two methods: the Dunlop method in which a felt pad is carefully molded around the elbow joint and gentle right angle traction is applied; the other method, skeletal traction, in which either a simple coat-hanger type screw or a wire is carried through the olecranon. This method reduces the swelling and permits access to the elbow at a later date.

Because fractures of the elbow joint are often associated with disturbances of epiphyseal growth around the elbow joint, it is impossible to predict the ultimate result. A consequent cubitus varus deformity may later necessitate an osteotomy at the level of the lower portion of the humerus.

Fractures of the Head of the Radius and Capitellum or of the Condyle. Fractures of the head of the radius and capitellum or of the condyle in which there is separation from the parent bone may require an open operation. When the fragments are large and not seriously displaced, early reduction is possible by gentle traction and pressure and immobilization by a cast. For smaller fragments displaced at angles of 90° to 180° careful exposure of the joint may be indicated for removal of the hematoma by washing, careful displacement

of the fragments, and reduction through the modality of a Kirschner wire or pin or screw fixation; the appliance may be removed later after complete healing.

Physical therapy is unnecessary for children, as has been explained. Tight casts, excessive manipulation, open operation at this site, other than for the exception described, and reduction under roentgenologic instead of clinical control—all these are without qualification so inadvisable that the necessity to avoid them must be stressed.

Fractures of the Clavicle. The shoulder joint must be immobilized. When displacement is slight or when only a narrow crack in the middle outer third junction is observed in the roentgenogram, then a soft tissue bandage around the arm and chest wall, held in place by adhesive tape, is sufficient. It is difficult, however, to keep such a bandage on an active child. An alternative is the use of a figure-of-eight bandage around both shoulders.

When the child is unusually active, a roll of plaster may be worn over the chest wall and arm which have first been well padded. This is worn for several weeks. A callus may be observed after treatment but it soon disappears. Several canvas belts are also available as aids to immobilization of the clavicle by external rotation of the shoulder. These are preferable to adhesive tape when the skin is sensitive.

Fractures of the Leg. Fractures of the leg may be divided into those of the tibia, those involving both bones, and those of the fibula alone. They may occur at any level, and if present in and about the joints, may also cause, however rarely, some epiphyseal injury. As a rule, these fractures can be reduced under general anesthesia, but should be done only when the patient's stomach is empty, even if this means a delay of several hours. A circular well fitting cast is applied after the knee has been flexed at a 15° or 20° angle and the foot has ben placed in neutral position. The toes of the foot should be left exposed for observation of the circulatory color. In epiphyseal injuries associated with the fractures of the leg, repeated roentgenologic studies should be made and measurements taken to ascertain the loss in the length of the leg. In treating fractures in children, notwithstanding the high degree of self-correcting, through growth of the epiphyseal sites, even of a seriously deforming fracture, the surgeon must not relax his diligence in attempting to reduce fractures without trauma to soft tissues and with every safeguard against excessive loss of length. He must at the same time correct rotation and angulation of long bones. He must apply a well fitting, well padded cast to obviate vascular and neurologic complications.

Fractures of the Femur. Bryant's traction method is the usual treatment for fractures of the femur in newborns or infants; or, in the case of newborns, a spica cast may be applied. Both legs should be carefully padded, moleskin applied judiciously, and the elastic bandages encircling the leg applied with the utmost caution and without pressure. Hospitals always have on hand the overhead bar necessary for traction. Do-it-yourself type overhead bars are available for use at home at surgical supply houses.

Whoever is in attendance — mother, nurses and physicians — must watch closely for any changes in the circulation of the feet during Bryant's traction treatment. Ischemic fibrosis does not happen often, but when it does, the problem is serious. Possibilities to guard against are: relative ischemia from hyperextension at the knee joints during this treatment and from compression of bandages; Volkman's ischemic contracture of the leg and irreparable injury to calf muscles; secondary changes in the form of deformities and attendant neurovascular disorders; and gangrene. Such complications may occur even on the normal side, so that both the fractured leg and the opposite one must be watched and traction removed without delay at the least suggestion of circulatory impairment.

Under normal progress, traction is continued for four to six weeks, after which it is replaced by a short spica

cast or soft tissue bandaging.

For older children, from 6 to 12 years of age, the conventional Thomas splint traction or Russell traction is suitable. It is not essential to reduce completely the fractures of the shaft of the femur. Side-to-side bone contact gives excellent result. Shortening corrects itself in time in almost all cases. Only rotation and angulation must be prevented.

Arterial and neurological complications are no longer so common as they were in the days of the wagon wheel injuries which were often fractures of the lower third of the femur in which there was a sharp spur which caused the injury to the popliteal vessels. The vascular supply to the hip in infants and children nevertheless may be so disturbed in the presence of fracture as to produce a septic necrosis, irregularity of growth, and shortening from epiphyseal arrest.

Open reduction may have to be resorted to when the neck of the femur has been fractured. This is one of the exceptional conditions under which open reduction may be indicated. When it is, skillful surgical technique is mandatory if permanent and serious problems of arrested growth are to be prevented. This is likewise true in reducing fracture fragments in and about the knee joint. Open reduction, furthermore, may be necessary for fracture of a single condyle of the femur when the fragments are displaced; however, most fractures of this type, including epiphyseal displacements and metaphyseal fractures, may be reduced under careful and steady traction on the fracture table, after which a spica cast must be worn from eight to twelve weeks.

So-called plating of fractures of the femur is contraindicated under all circumstances, because of the danger of serious complications. Fractures of the femur in children heal well with early and adequate restoration of length. The growth pattern is gauged and followed by roentgenograms taken from the head of the femur to the lower condyles of the femur.

Regarding compound fractures of the femur, as of other bones, cleansing and debridement must be thorough but careful so as not to remove any of the bone. Washing and irrigating do not mean removing and destroying.

There are numerous other fractures that have not been mentioned. This presentation was not intended as an exhaustive or comprehensive review. Some basic principles for general application may be helpfully stressed, however:

Basic General Considerations

1. Preoperatively, the child who is old enough to understand should be told about the fracture and reassured about what is to be done, including forewarning about premedication by injection. By gentle and kindly treatment, the child will understand the prerequisites and will co-operate.

2. Inasmuch as metabolism of bones is dominantly active in youth, natural longitudinal growth aids correction of fractures near the epiphyses. Repositioning or reformation in and about the joints is relatively simple regardless of how severe the deformity appears in the roentgenograms. It is not only unnecessary but contraindicated to try another reduction every two or three days when repeated roentgenograms continue to show deformity. In the developing epiphyses of children, given time, after the initial reduction by the surgeon, self-correction may be anticipated. On the other hand, the irritation and disturbance set up by overmanipulation through repeated attempts at reduction delay healing, invite complications, and give a poor end-result. It is the clinical condition of the joint in the young patient that determines the continuing treatment; one does not treat the defect observed in the follow-up roentgenograms but the patient. At the same time, however, the surgeon must be aware of the necessity of correcting angulated or rotated fractures and those that have produced shortening—these must be reduced and cannot be left to time and natural repair.

3. Fractures in children rarely require an open operation. The days of femur-plating, pin insertion in and about the joints, or even skeletal traction in and about the joints are almost over; such

methods have been largely replaced by careful and diligent reduction during which the soft tissues, including the nerves and blood vessels, are likewise appropriately treated and gently handled. Well aligned bones in well functioning joints cannot result without attention to the blood supply. For the same reason, casts and elastic bandages and dressings should be applied loosely, without pressure, if intractable, incurable dystrophies and permanent deformities of the extremity are to be prevented. Ischemic contracture of the extermeties of infants and children is still too frequent as a result of Bryant's traction for fractures of the femur.

4. Compound fractures call for careful cleansing, thorough but gentle debridement, and primary suturing. Replacement of lost blood and appropriate antibiotics insure better results than formerly, provided the antibiotics are not relied on to displace the strictest aseptic control.

5. Preparation of the emergent patient must be thorough and not haphazard in the haste to correct the fracture. It is far better to delay correction of the deformity if the patient's stomach is full, because under anesthesia this may have grave consequences: regurgitation of food, lung abcess, sepsis and death.

6. Hidden or occult fractures must not be overlooked. They can be detected by comparative bilateral roentgenograms and by repeating the roentgenologic survey two or three days after the initial survey. The later roentgenograms may disclose a fracture line that was not at all apparent at first.

7. An orthopedic examination is not complete without a review of the vascular and neurologic systems. Injuries of and about the shoulder and neck may be associated with lesions of the brachial plexus and therefore demand careful review of the peripheral nerves as well as a vascular survey in which the color of the skin and pulse rate are certainly recorded as minimal data. Vascular complications in association with fractures may include a hematoma which exerts pressure on a large blood vessel, intramural hemorrhages of vessels, false dissecting aneurysms or arteriovenous aneurysms.

8. Because orthopedic problems are often handled under emergency conditions, surely for the welfare of the patient but realistically for self-protection against the omnipresent threat of malpractice suits, every effort at eliciting a detailed history should be made and carefully filed in the hospital records.

VASCULAR TECHNIQUE —

(Continued from page 72)

gives best results in mounting sections or whole specimens.

The method discussed above was devised for use with embryos. However it may be used for any very small over all structure in which it is desirable to show patterns of vessels which cannot be made out easily by the unaided eye.

We illustrate the result of our method by a photograph of a typical 300 mu unstained section of a preparation of a 16 day, 0 hour, 16 mm rabbit fetus. Observe the perspective. Notice the clarity of the margin of the cup. The vitreous (hyaloid) circulation, its retinal plexus in the hyaloid membrane, and hyaloid artery are readily apparent. The hyaloid artery is embedded in the optic nerve which is invisible, because of its transparency. The exit of the nerve from the retina however is outlined by the vascular net of the optic cup. The exit shows as a transparent long ellipse around the most constricted portion of the hyaloid artery. The definition of the sectioned retina and lens, is shown with uncommon precision.

SPHINCTER PRESERVING RESECTION VS. ABDOMINAL-PERINEAL RESECTION FOR CARCINOMA OF THE RECTOSIGMOID COLON

WILLIAM SCHUMER, M.D.*

At present, the great controversies in cancer surgery pertain to the radical versus conservative approach as exemplified by the discussions in breast and thyroid cancer surgery. The differences in atttitudes toward breast cancer therapy between McWhirter and the American school (Haagensen, Urban and Wangensteen) and those of thyroid surgery as stated by Crile and H. E. Martin, are well known to all of us. These controversies and differences indicate more strongly that the surgeon is certainly not satisfied with the present therapeutic results in cancer. The newer techniques for the most part, are attacking the problem at diverse poles. Crile and McWhirter are trying to do the least amount of surgery in certain cancers because they feel that the biological predeterminism of the tumor is the crux of the problem, while Urban and Wangensteen are extending cancer surgery to more and more lymph channel dissections. The pendulum swings further and further away from the center both radically and conservatively. In the discussion of the pros and cons of sphincter preserving surgery and abdominal perineal resection, we are not dealing with a complete shift to conservatism, but in a shift to moderation and modification. In order to understand the problem, let us follow the evolution of the abdominal perineal resection as developed by Miles.

Up to 1908, when Miles described the abdominal perineal resection, the attack on rectosigmoid cancer was strictly a perineal effort. There was the Kraske procedure which limited itself to the removal of the rectum without removal of the levator ani and perianal tissues. Then Miles studied the spread of cancer of the rectum and found that there were three avenues of lymphatic metastises: (1) downward spread intramurally; (2) lateral spread into levator ani and perianal tissue; (3) upward spread into the pelvic mesocolon following the blood supply of the rectosigmoid. In explanation Miles wrote, "I ultimately arrived at a removal which was the most complete it was possible to carry out from the perineum. Failure to prevent reoccurrences was due to the fact that tissues of the upward zone of spread already invaded, lay beyond the reach of any operation carried out solely from the perineum. The tissues representing the axilla in cases of cancer of the breast, can be approached only through the abdomen and, therefore, it is obvious that the attempt to excise the cancerous rectum from the perineum is as futile as amputating a breast affected by cancer without also clearing the axilla of invaded lymph glands". It would be well to keep the ways of metastatic spread in mind as we continue our study, for herein lies the basic tenets of the controversy. From the conclusion stated above Miles devised the abdominal perineal resection, which included removing one half or more of the sigmoid and the whole of the rectum with its lymphatics; the peritoneum lining the floor and walls of the pelvis; the whole of the levator ani and coccygeus muscles; the whole of the anal sphincter muscles, as much as possible of ischiorectal fat; and as wide an area of perianal skin as possible. The first part of the operation is carried out through the abdomen taking the sigmoid colon, rectosigmoid and rectum and their respective mesocolon (lymphatics). Usually the dissection from above ends when the prostate in the male and cervix in the female is reached anteriorly and the tip of the coccyx posteriorly. The second portion is the perineal dissection where the perineal skin, fat, levator ani and rectum are resected. In the 49 years which have elapsed since the above description, no *basic* change in this concept of technique has occurred. There have been recent radical modifications as de-

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scribed by J. Baker and P. Rossi who maintained that metastatic carcinoma occurred higher along the left mesocolon. They therefore, resect the whole descending colon and make transverse or splenic flexure colostomy.

Now let us swing the pendulum to the conservative side. Let us consider the reasons why some investigators feel that sphincter preserving resections are adequate in the treatment of cancer of the rectosigmoid. To refresh the readers' memory as stated above the crux of the controversy is in the description of lymphatic spread. First, consideration of the downward lymphatic spread is indicated. Miles in his description of the downward spread of carcinoma of the rectum wrote: "It is a very difficult matter to detect such isolated cancer cells even when a large number of serial microscopical sections have been made, but their presence has been revealed often enough to establish the fact beyond doubt that their structures are liable to be invaded during the process of dissemination". In the light of the more recent work done by McVey, Westhues, Gabriel, Dukes and Bussey, Gilchrist and David (1947) Coller, Kay and MacIntyre and Grinnell, it was noted that there was spread in four cases of cancers of the ampulla of the rectum and in three cases of cancer in the upper rectum and recto sigmoid. All three of the latter were within 1.5 cm. of the lower edge of the tumor. Glover and Waugh in a study of 100 cases found that there were 36 incidents of retrograde spread, but only three were more than 2 cm. distal to the edge of the lesion. Waugh and Glover also pointed out that "if all instances of retrograde spread of more than 2 cm. distally to the lesion which are reported in the literature are added, the sum total is 4 out of 339 specimens with nodal involvement which were studied, and would give an incidence of just over 1%. Since nodal involvement is found in one-half the cases, this figure drops to 0.5% when all cancers of this region are considered. Is it then advisable to subject all patients with rectosigmoidal cancer to a Miles operation with a permanent colonic stoma when only 1 in 200 will have significant retrograde spread? Furthermore, is it feasible since it is doubtful whether such a patient can be cured by the Miles operation or by any other surgical procedure?"

Spread to levator ani was definitely described by Miles in his 1931 article, "the levator ani are especially prone to invasion of cancer cells which have gained access to extra-mural lymphatic system, so that they should be completely removed when a cancerous rectum is excised." However, Waugh and Glover in the same study described above, found only one case in which the levator ani muscle was involved. In this case the rectal wall was perforated and it was concluded that the spread was by direct extension, and not by lateral spread over the lymph vessels. Guernsey, Waugh and Dockerty also at the Mayo clinic found only one case in 210 rectal cancers where the lesion extended through the rectal wall to within 1 mm. of the insertion of the levator ani. No instance of lateral spread to levator ani along lymphatics or direct extension could be found.

Further work by Waugh and Black revealed that the maximal distal intramural longitudinal spread for cancers of the rectosigmoid was 3 mm., for sigmoidal lesions 4 mm., and for carcinoma of the descending colon 12 mm. It was concluded therefore, that if the surgeon were to remove 2-5 cm. (2 inches) of rectum, distal to the lesion, he would be assured of complete removal. Waugh, however, suggests that it would be "good practice for a competent surgical pathologist to check the specimen immediately and examine carefully the distal cut edge grossly, and under the microscope" If there is any question of the "adequacy of the margin", it would be better to convert to a Miles procedure i.e. remove the distal segment (rectum) completely.

Thus the Mayo clinic group has come to the conclusion that if downward spread via lymphatics and longitudinal extension into the levator ani muscles are not significant in certain areas of the rectum, then the Miles procedure can be modified. The modification is to resect only 2 inches below the lesion; not to remove extensive amounts of perianal tissue (external sphincter) and perirectal tissue i.e. levator ani. In other words,

to do as much sphincter preserving as possible in those lesions above 5 cm. from pectinate line or levator ani muscle insertion. Dr Waugh has recently stated he would *do* a Miles abdominal perineal resection on those 25% of cancer of the rectum which are 5 cm. or less from the pectinate line. Guernsey found, that in lesions in this area, approximately 40% involve the internal sphincter, that is an extension through the bowel wall and chances are good for further spread into the perineal tissues as described by Miles. For those cancers 5-10 cm. above the pectinate line he would do a pull through operation, either saving the anus and lower 5 cm. of the rectum as B.M. Black does or removing the entire rectum below the lesion and saving the external sphincter. For those lesions 10 cm above the pectinate line, he does an anterior resection and anastomosis.

The anterior resection per se, is a resection of the lesion according to the lymphatic precepts, which were described above, and anastomosing the end of the descending colon, usually to the segment of the rectum left.

The pull through begins the same way as the Miles abdominal perineal resection. Abdominally the rectum is dissected from its sacral bed, the lateral ligaments cut and ligated (middle hemorrhoidal vessels); the rectum is freed anteriorly to the cervix or prostate; and posteriorly to the tip of coccyx. Then, through careful perineal dissection the ano-rectum is taken from the external sphincter and then the levator ani is cut away. The whole of rectum, recto-sigmoid and sigmoid is pulled through the dilated external sphincter until the area which was chosen as the end of the resection is reached. The bowel is then anchored by suturing fat tags to the perineal skin and the withdrawn sigmoid and rectum is excised over a Payr clamp. The above description is cursory and the author would suggest reading Dr. Waugh's excellent description of the surgery for further details. There are other similar techniques of the pull through procedure which tend to preserve the 5 cm. anal rectal canal, because it is felt that continence is better controlled with preservation of the internal sphincter. These procedures are described by B. M. Black, Swenson, Babcock and Bacon, and R. R. Best.

The comparison of survival rates between Miles abdominal perineal resection and sphincter preserving techniques reveals that there is no significant difference statistically. Miles abdominal perineal resection gives a 75% 5 year survival rate without positive nodes and a 25% survival rate with nodes giving an overall survival rate of 51%. Pull through gives an overall survival rate of 53% and anterior resection surgery gives an overall survival rate of 65%. The latter statistical figures are based on Waugh's work of sphincter presering surgery for cancer of the rectum. The morbidity and mortality of both procedures are comparable in incidence and type.

We have discussed the arguments both for and against each of the procedures and it will be time and more experience with abdominal perineal resection and pull through resections from many investigators, that will give us the key to the right door. We must, however, as J. H. Mulholland stated "assure ourselves that the operation is at least as complete from the standpoint of removal of lymphatics as the abdominal perineal resection operation is, and therefore represents no compromise with attempts to cure the cancer". However, one who has ever done a Miles abdominal perineal resection, cannot help but hope that the Mayo clinic studies and statistics hold up in the court of surgical opinion.

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CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. L. CARDON, Chairman | **DR. H. RAPPAPORT, Secretary**
S.L. No. 290409 and 291366 | **DR. F. R. SWIATEK — Service**

March 28, 1958
A—153—57

1st Adm.: June 29, 1957—July 12, 1957:

A 14 year old, white male 7th grade student, was admitted because of jaundice and abdominal swelling. Three weeks prior to admission, he developed a "cold" with some elevation of temperature, cough, occasional vomiting after ingestion of fatty food, anorexia and upper abdominal pain. Following this, he noticed swelling of the abdomen and more severe nausea and vomiting. A week after admission, he developed jaundice with dark urine and stools, but had no pruritis or fever. During the past few days, nausea had subsided; patient noted a gain in weight of 6 pounds.

He was seen by a physician at the age of 6-7 years because of an upper respiratory infection. The physician stated that he had a "large liver." The mother said that her son had always been on "the heavy side" and that he had grown quite noticeably in height during the last year. Prior to the onset of the present illness, the patient was given three injections of polio vaccine. No one else, known to the patient had an illness similar to the present one.

PAST HISTORY: Uncomplicated childhood diseases. No allergies reported.

FAMILY HISTORY: Two siblings; mother and father in good health. A grandmother had diabetes mellitus.

PHYSICAL EXAMINATION: temperature 99.2°; resp. 20; pulse 92; blood pressure 135/75. Weight was 220 lbs. and height 6 ft. The patient was alert, cooperative and appeared to be in no acute distress. There was generalized icterus of skin and sclerae and a two plus pitting edema over all his body. The pupils were equal and reacted normally to light and accommodation. The eyegrounds were normal; the tongue slightly coated. Chest: some dullness over the right lower base posteriorly with decreased breath sounds. The left lung was clear. Heart: negative. Abdomen: distended, with signs of free ascites. The liver was felt and percussed four fingers below the costal margin in the mid-clavicular line and was non-tender with a firm edge. The tip of the spleen was felt; a large ecchymotic area was noticed in the left thigh by one observer.

HOSPITAL COURSE: The patient was afebrile, complaining of anorexia. He was treated with low-salt, high-protein, high carbohydrate diet, parenteral administration of mercurial diuretics, daily crude liver injections and multi-vitamins. The patient was discharged, improved, with a loss of seven pounds of weight.

2nd Admission
July 24, 1957—August 15, 1957:

The patient was readmitted with complaints of weakness, anorexia and an increase in abdominal and peripheral swelling.

On physical examination, the patient was ambulatory and appeared to be in no acute distress. Temperature 99.2°; respiration 19; pulse 90 and blood pressure 120/70. The yellowish discoloration of the skin and sclerae was more pronounced; there was ascites and a 3+ pitting edema.

HOSPITAL COURSE: On the day following admission, paracentesis yielded 9000 cc. of clear yellow fluid — specfiic gravity of 1.008; total protein—0.5 gm%. On the 3, 5 and 7th day, 12.5 mg of salt-poor aqueous solution of serum albumin was given intravenously, with improvement of peripheral edema. The liver and spleen seemed to decrease in size. The patient was having loose bowel movements with vague abdominal complaints, little relieved by Kaopectate. He was ambulatory. By the 12th day, reaccumulation of ascitic fluid was noted, and serum albumin was started and given every other day. On the 15th day,

LABORATORY DATA - 1st Adm:

Bl.Cts:	Hgb.	RBC	Hemat.	WBC	Polys	Lymphs	Monos	Eos	Retic. Count	Platelets
6/29/57	11.1Gm	3.91	36	4,100	56	44	-			decreased
7/1/57	11.6Gm	3.52	35	2,950	65	29	3	3		84,000
7/5/57				1,950	56	40	3	1		70,000
	Coagulation time - 14 minutes; bleeding time - 4 minutes.									
7/9/57	11.6Gm	3.94	33	2,900	44	54	2		1.7	91,000
7/11/57	12.9Gm	4.09		4,050	79	15	6			

	Proth. Time	Clott. Activity	Infectious Mononucleosis
6/29/57	33 sec.	12%	
7/1/57			Neg.

Fragility Test RBC	Begin. Hemolysis	Complete Hemolysis
Patient	.42%	not complete in .21%
Control	.42%	Control .29%

Chemistry:	Glu.	BUN	Bilirubin Tot.	Bilirubin Dir.	Thy.Turb.	Ceph. Flocc.	Cholest.	Esters	T.P.
7/1/57	78	14	3.3	0.9	11.0				6.1
7/2/57						4+	288	67%	
7/5/57		12							
7/11/57					10.2	4+			

	Alb.	Glob.	Phos. Alk.
7/1/57	2.1	4.0	17.2

	B.S.P.	Sed. Rate	GOT	Na	K	CO_2	Cl.	Blood Ammonia
6/29/57		14						
7/1/57	46%			143	4.0	22	104	
7/5/57			14					101 gamma%
7/9/57				135	4.1	27	103	

	Globulin Fractionation Alpha	Beta	Gamma	Cholest.	Esters	T. Pro.	Alb.	Glob.
7/11/57	1.4	0.9	1.4	245	59%	5.2	1.5	3.7

tarry stools were reported, and the patient was given two units of packed red cells in a 72 hour period. On the 19th day, the patient developed sharp pain across the lower abdomen without nausea or vomiting. Blood pressure was 104/0; pulse 106 and regular; respiration 32; temperature 100°. The lungs were clear and the heart tones rapid but regular; no murmurs heard. The abdomen was distended, and bowel sounds were decreased. Rectal examination revealed bright red blood. A Levine tube drained dark-grey fluid. The patient became somnolent and more jaundiced, with constant nausea, loose dark green stools and deeply bile-stained urine. I.V. Fluids were given daily (about 2500 cc. of 10%

Urinalyses:	Sp. Gr.	Glu.	WBC	Cryst.	Bile	Urobilinogen
6/29/57	QNS	tr.	3.4	oxalate		
7/2/57					neg.	2.2 Ehrlich units
7/5/57					neg.	7.1 mg/24 hrs.
7/9/57	QNS		occ.			

	Stool Guaiac	Stool Urobilinogen
7/5/57		14.9 mg./24 hrs.
7/9/57	4+	

Direct Coombs - weakly positive.

Cold Agglutinins - 8 units.

Bone Marrow: 7/3: erythroid hyperplasia, normoblastic type.

X-ray - Chest: 7/8: The cardiac silhouette is normal. Some prominence of the right hilus is seen. However, there is no evidence of glandular enlargement. The mediastinum is not widened. The lungs are essentially clear.

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glucose in water with hydrocortisone added, 50 mg per bottle). The patient's condition became progressively worse, with increased lethargy; he remained afebrile. On the 22nd day, tarry stools were noted, mixed with bright red blood in an almost continuous flow. He had a small amount of hematemesis and expired soon thereafter.

Dr. F. R. Swiatek: This is a high school boy who was seen in the office on June 12, 1957. For two weeks he had complained of lower abdominal pain which was not definite, not radiating, not related to bowel movements or the G.U. or G.I. system. He had some nonproductive cough. Physical examination was entirely negative at the time except for a large abdomen and prominent veins in the skin of the back, and I noted too that the urine was dark and contained bile. There were no red cells, white cells, casts, albumin, or sugar. I discovered he had a bilirubin of 1.9 and a secondary anemia. I decided then to hospitalize him. After being thoroughly worked up with a diagnosis of cirrhosis of the liver, advanced stage, he was given the usual treatment of cirrhosis of the liver; he was tapped, and he went on very rapidly and died.

Chairman: Dr. Einhorn, would you care to comment?

Dr. Einhorn: This case presented some very interesting and unusual features. From the clinical history it was evident that the patient had a period of symptomatology consistent with hepatitis. However, when he was seen by us he presented the picture of a full blown cirrhosis. The most conspicuous feature on physical examination was the massive edema. In addition to this, laboratory studies revealed an anemia and a severe thrombocytopenia. Our speculation at the time was that this boy initially had acute hepatitis which developed into the type of hepatitis characterized by fulminating necrosis, rapid death, and an autopsy specimen would reveal acute yellow atrophy. We felt the disease process followed a subacute course and eventually resulted in a post necrotic type of cirrhosis. The clinical features of the case were no doubt due to a severe hepatic insufficiency and portal hypertension with an accompanying splenomegaly. It was our opinion that the anemia and thrombocytopenia were preceded by a hypersplenic mechanism.

Chairman: Dr. Nadelhaft, do you have any X-rays to present?

Dr. J. Nadelhaft: The chest films show a normal heart and lungs, and the diaphragm is elevated in relation to the large abdomen, the cause of which was determined clinically to be ascites.

Chairman: The case is now open for general discussion. Any comments? Dr. Zimmerman.

LABORATORY DATA - 2nd Adm:

Bl.Cts:	Hgb.	RBC	Hemat.	WBC	Polys	Lymphs	Monos	Eos.	Platelets
7/25/57	10.8	3.81	32	2,350	82	8	6	4	adequate
8/5/57	10.4	3.16	30	2,750	72	22	3	3	65,000
8/12/57	13.3		42	8,450	83	4	13		
8/15/57	5.6	1.49							adequate

	Proth. Time	Clott. Activity
8/12/57	65 sec.	10%

Chemistry:	Glu.	BUN	Bilirubin Tot.	Bilirubin Dir.	Thy. Turb.	Cph. Floc.	Cholest.	Esters	T.P.	Alb.
7/25/57	60	8	5.2	1.8	10.6	4+	253	57%	6.2	1.8
8/5/57			4.0	1.5						
8/15/57			28.8	16.0						

	Glob.	Phos. Alk.	B.S.P.
7/25/57	4.4	9.2	62%

Additional Chemistries:	Tot. Pro.	Alb.	Glob.	A/G
8/6/57	5.1	1.6	3.5	0.5
8/15/57	3.6	1.1	2.5	0.5

7/25/57: $Alpha_1$ Glob - 3.7%
$Alpha_2$ Glob - 3.7%
Beta 14.1%
Gamma 49.5%

8/15/57: Blood Ammonia 164 gamma%

8/12/57: Na-128; K-5.2; Cl-105

Urinalysis:	Sp.Gr.	WBC	Urobilinogen	Bile	Protein
7/25/57	1.011	occ.			
8/8/57	1.016	few	strong. pos.		
8/13/57	1.011			pos.	neg.

	Stool Guaiac	Stool Culture
8/6/57		neg.
8/8/57	4+	
8/12/57	4+	neg.
8/13/57	4+	
8/15/57	4+	neg.

Dr. Zimmerman: First, I quite agree with the diagnosis, that this patient appeared to have a post necrotic cirrhosis and that at the onset the clinical picture was consistent with hepatitis. I think that one of the blocks clinicians often get in considering cirrhosis, either post necrotic or Laennec's, is trying to point to a single clinical picture whereas either disease has to be considered dynamically. There can be a healed post necrotic cirrhosis with little or no actual necrosis where the features are largely those of parenchymal loss in terms of hepatic

dysfunction and of marked portal hypertension. On the other hand, there can be a very active post necrotic cirrhosis with active necrosis and features which have been called subacute hepatic necrosis. This patient would appear to be in that category with subacute hepatic necrosis, sub-chronic hepatitis or a mixture of these features. Clinically, and in this there is general agreement, that this is a post necrotic cirrhosis with active necrosis. This can occur quite rapidly. I think you may remember the report of Lucke in 1944, wherein he studied a large group of patients with fatal serum hepatitis. All in this group had survived at least 30 days. Many survived a month or two. There was evidence of cirrhosis in almost all of them with varying degrees of necrosis at the same time. I would like to comment on the bleeding tendency this patient showed. There is not only a thrombocytopenia, but a prothrombin time of 33 seconds. We should remind ourselves that in this prolonged prothrombin time we have in a sense a wastebasket. Deficiency of labile factor, stable factor, prothrombin and P.T.C. have been demonstrated in patients with hepatic disease. There are multiple causes of bleeding in patients with this type of disease, including as a matter of fact, excess fibrinolysis in which the clot, after being formed, is lysed.

Dr. Rappaport: How do you explain the thrombocytopenia?

Dr. Zimmerman: The elements of portal hypertension in this patient were not striking. As I recall the autopsied spleen it wasn't strikingly enlarged. Splenomegaly is by and large a more striking feature in post necrotic than in Laennec's cirrhosis. Nevertheless, I think it is a perfectly fair formulation that Dr. Einhorn gave us, but I would have liked to have seen a bigger spleen.

I might say one more thing about juvenile cirrhosis. Some of you may have seen a report in General Medicine a year and a half ago — Wilson's disease in a patient with what was at first thought to be hepatitis. I happened to see that patient several years before Chalmer's group studied her, and reported her. She presented with post necrotic cirrhosis, with a history of having had acute jaundice four or five years before. We considered this cirrhosis an unusual sequel of hepatitis. It was only after her brother developed neurological symptoms that she was diagnosed as Wilson's disease. She was restudied and found to have Kayser-Fleischer rings, and several neurological abnormalities. A number of things to keep in mind in cirrhosis in this age group even though the history doesn't suggest it are the metabolic abnormalities such as Wilson's disease, Fanconi's syndrome associated with post necrotic cirrhosis perhaps because of a urinary loss of the sulfur containing amino acids.

Chairman: Are there any comments?

Dr. H. Isaacs: First, the findings of dullness of the right base is due undoubtedly to compression atelectasis from a large liver, and I have seen patients with gallbladders with quite similar temperatures and with slight compression atelectasis of the right base diagnosed as pneumonia rather than gallbladder disease or liver disease whatever it happens to be. Secondly, I believe the cause of death here was hepatic trauma which might have been precipitated by any of three factors. One, the G.I. bleeding; two, the paracentesis; and three, which I think is important, I notice in the blood count on the last page the white count went up from 2700 to 8400 with an increase in Polys from 72% to 83% which makes me think he had an infection, most likely a pneumonic process.

Chairman: Dr. Mandel.

Dr. Mandel: One of the questions which occurred to me was whether there was an acute onset of this patient's liver disease just prior to his first admission or whether he had some pre-existing liver disease, as suggested by his mother's statement indicating previous enlargment of the liver. Also, this 15-year-old boy was quite large: 6 feet tall and 220 lbs. in weight. It is possible that he had had cirrhosis of either of the types mentioned though in an asymptomatic form, which is not too unusual, or that he had a fatty liver. This acute episode might then have to do with an extra-hepatic infection, or, in other words, it may represent an acute hepatocellular necrosis superimposed

upon chronic liver disease, precipitated by a respiratory or other type of infection. This is not uncommon in alcoholics with fatty liver or in cirrhosis but it is quite uncommon in patients with fatty liver associated with obesity but without alcoholism.

The other point I would like to make is that the generalized anasarca in this patient reminds us of experiments involving plasmapheresis in dogs and other animals, comparable to a state of nephrosis without albuminuria. The marked reduction of serum albumin in this patient is partly due to inadequate formation in the liver, partly due to "albuminuria into the peritoneal cavity." Intravenously injected albumin will likewise find its way readily into the peritoneal cavity and therefore be of little help in raising the serum albumin level.

Chairman: Are there any other comments, questions or discussion? If not, I would like to make some comments. I would agree that we are dealing with a case of hepatic cirrhosis here. However, in the interests of a complete differential diagnosis I think another possibility should at least be mentioned. We have here a 14 year old boy whose illness began with a "cold," fever, cough, anorexia, occasional vomiting after injection of fatty foods, and upper abdominal pain. Following this there appeared abdominal swelling, severe nausea and vomiting, marked jaundice, ascites, a progressive downhill course, and death. In these circumstances one may consider the possibility of spontaneous hepatic vein thrombosis, or Chiari's syndrome.

I would like to take this opportunity, too, to mention another point. At the medical seminar Wednesday the question came up about the leukocyte count in hepatitis and hepatic necrosis. I reviewed the cases of hepatitis and acute and subacute atrophy of the liver in the Cook County Hospital Compendium of Pathological Conferences by Dr. Richard H. Jaffe. Of 9 cases in which the WBC was recorded it was 11,000 in two; 14,000 in two; 16,800 in two; 28,000 (with 84% neutrophiles) in one; 36,000 in one; and in only one was the count as low as 7,200. Dr. Jaffe was of the opinion that infection was a factor in most if not all of these cases; and that in some streptococci might be responsible. Only one of these cases (with a WBC of 11,000) was definitely a case of leptospiral hepatitis (Weil's disease) and another (with a WBC of 14,000) probably so. In any case, in this group of cases leukocytosis was the rule rather than the exception.

Dr. Zimmerman: We studied a large group of patients overseas with hepatitis. The highest leukocyte count found was 12,000. 95% of the patients had values below 10,000. We had one patient whose white blood cell count was above 12,000. He had a documented beta-hemolytic streptococcal pharyngitis. I would say that in infectious hepatitis a leukocytosis would be quite surprising. The implication of leukocytosis in apparent hepatitis is that it has been misdiagnosed or there is a complication. Certainly one should think of leptospirosis. Another cause of striking leukocytosis in patients with acute jaundice is the acute phase of alcoholic fatty metamorphosis with jaundice that we call steatonecrosis and that has been called florrid cirrhosis or alcoholic hepatitis. In these patents there is a surprising leukocytosis. Other complications of cirrhosis which may cause leukocytosis are hepatoma, necrosis, or pneumonia. Although these are valid considerations, leukocytosis is common in jaundiced cirrhosis even without demonstrable infection. With respect to the possible role of streptococcal infection in hepatic injury which has been mentioned in the literature, it is our impression that this is a poorly documented phenomenon.

Chairman: Dr. Bowerman, will you give the autopsy findings?

Dr. Bowerman: At the time of the autopsy it was observed that the patient was quite tall for the age of 14, measuring at least 6 feet tall. The abdomen was markedly protuberant, resulting from the accumulation of clear ascitic fluid totaling 9,000 ml. There was no fluid in the pleural cavities. The heart and great vessels showed no distinctive abnormalities. The lungs showed only patchy scattered areas of atelestasis. The question of compression atelectasis was raised, but actually this was rather widely scattered throughout both the

upper and lower lobes, although possibly there was a little bit more in the lower lobes. There was no evidence of a pneumonitis. The liver (Fig. 1) weighed 1450 grams. We would have expected a heavier liver in a normal patient of this weight and size, but certainly the decrease in size is not great. It is obvious that the liver is composed of many nodules of varying size. They vary greatly in size, and some of them measure up to a couple of centimeters. They are lying imbedded in what appears grossly to be a very abundant fibrous scar tissue. The predominant color is a greenish-yellow. You will notice that some areas have darker centers in the nodules; others are lighter. We are therefore dealing with some form of hepatic cirrhosis. I am going to abandon the liver for the time being and discuss some other aspects of the case and return to it later for a more detailed discussion. The G.I. tract was examined with great interest because of the history of gastrointestinal bleeding. The esophagus showed no definite diagnostic abnormalities on gross examination. The conventional method of studying the esophagus in cases of cirrhosis needs improvement. A method that is currently employed in one of the local Veterans Administration Hospitals for the demonstration of esophageal varices would have been desirable in this case. However, careful inspection of the esophagus demonstrated quite conclusively that it was not the source of bleeding. When we looked at the stomach we saw near the greater curvature several small superficial mucosal ulcerations (Fig. 2) measuring up to 0.6 cm. in greatest diameter. The stomach contained approximately 2,000 cc. of red fluid blood. These gastric mucosal ulcerations were the only gross evidence of a bleeding source. The microscopic section (Fig. 3) shows that the depth of ulceration of the gastric mucosa is not that which is characteristically seen in what we might call the classic peptic ulcer. Here it is more superficial. However, in a patient with the hemorrhagic diathesis of severe liver disease, such even relatively superficial ulcerations may serve as a source of severe hemorrhage. Massive gastrointestinal hemorrhage has been reported from such ulcerations or even from gastritis in the presence of portal hypertension.

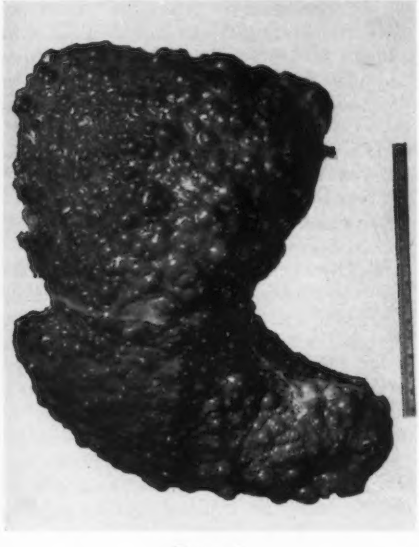

Figure 1
Liver, 1450 grams. Post necrotic cirrhosis.

Figure 2
Stomach. Multiple superficial mucosal erosions near greater curvature.

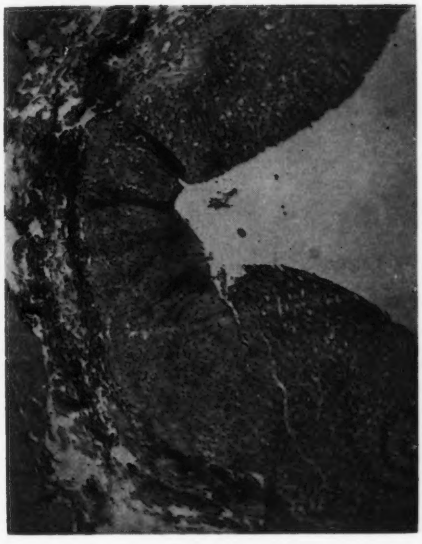

Figure 3
Acute superficial erosion of gastric mucosa. H. & E. 95X.

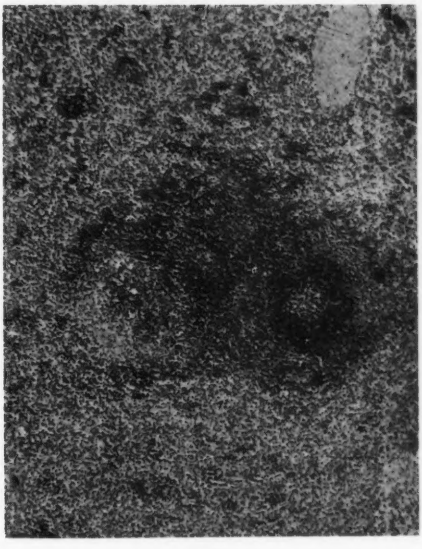

Figure 4
Spleen: Perifolliculer hemorrhage. The cords are diffusely thickened with secondary collagenization and reticulo-endothelial hyperplasia. H. & E. 105X.

The kidneys showed marked icterus, and although swollen, they did not appear otherwise abnormal. Each weighed 200 grams. Microscopic sections showed only scattered bile pigment casts in the collecting tubules. The term cholemic or biliary nephrosis has been given to such kidneys where bile may often be found in tubular epithelial cells in addition to the tubules, but it is generally felt that rarely does significant alteration of renal function occur in this lesion.

The spleen was firm and weighed 850 grams, making it from four to six times

Figure 5
Breast: Mild gynecomastia with hyperplasia of duct epithelium.

the normal weight. Sections of the spleen show the changes that we recognize now as characteristic of those occurring in the presence of portal hypertension and to which we give the term fibrocongestive splenomegaly. Here we see (Fig. 4) one of the many perifollicular hemorrhages that were scattered throughout. The cords are diffusedly thickened by secondary collagenization and formation of new fibers, and there is a diffuse hyperplasia of reticulo-endothelial cells. The functional effects of such a spleen may be anemia, thrombo-

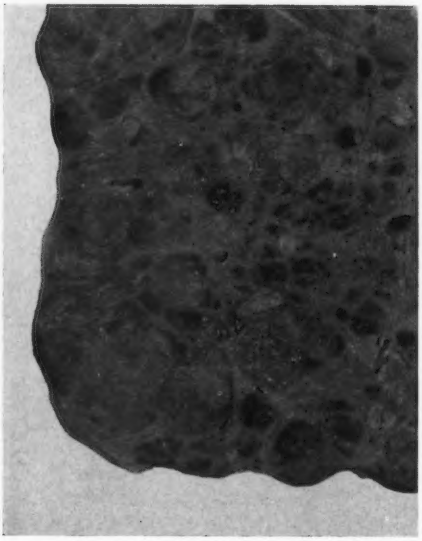

Figure 6
Liver: Regenerating parenchymal nodules separated by coarse bands of scarring consisting of collapsed framework.

cytopenia, and granulocytopenia. These effects are grouped under the rather broad term of hypersplenism due to fibrocongestive splenomegaly. The testes appeared on gross examination to be somewhat atrophic. With the body build and size of this patient at the age of fourteen we would have expected relatively normal sized testicles. Microscopically there is no evidence of any active spermatogenesis, and there is some mild fibrosis of the basement membranes of the seminiferous tubules. On gross inspection the breasts were not considered to be significantly enlarged. Histologically, however, there are present the changes (Fig. 5) which the surgical pathologist sees in cases of gynecomastia. The intraductal hyperplasia of this sort is quite characteristic, and such a histological change would not be unexpected in a patient where presumably there is a significant degree of the hyperestrogenism such as that present in advanced cirrhosis. I might add for those who are fond of eponyms in medicine that the triad of gynecomastia, cirrhosis, and testicular atrophy, like so many triads has been given the name of a syndrome: it is called the Silvestrini-Corda syndrome. The bone marrow shows the reaction that we would anticipate in the presence of a massive hemorrhage. There is a diffuse active hyperplasia which is predominantly involving the erythroid series, and is normoblastic in type.

In return to a more detailed study of the liver (Fig. 6) I wish to show this cut surface of the gross specimen to re-emphasize the marked variation in the size of nodules which we see separated by an abundant connective tissue. When the liver has been the site of extensive necrosis, the localization may be to a particular zone of the lobule, and if the patient survives and regeneration occurs, the lobular architecture may be reconstituted without significant distortion. When the necrosis is massive and is confluent between many nodules with concomitant total destruction of the lobular parenchyma, the more resistant structures such as the portal triads and supporting reticulum will collapse. Such a liver is often flabby and contracted with a wrinkled surface. To this the

Figure 7
Liver: Low power of regenerating nodules showing marked variation in size separated by collapsed framework and fibrocollagenous tissue. H. & E. 25X.

Figure 8

Liver: Broad connective tissue band containing proliferation of duct-like structures. H. & E. 105X.

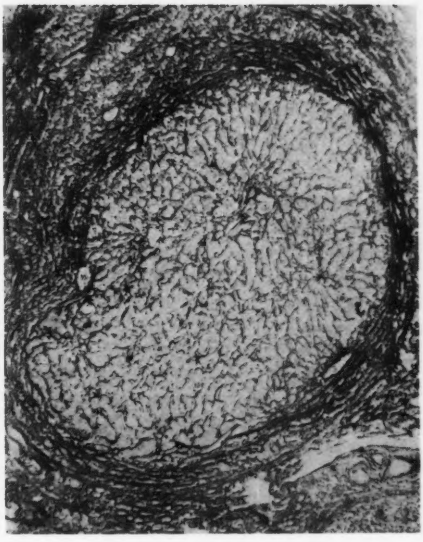

Figure 9

Liver: Regenerating nodule with compressed peripheral reticulum. Snook reticulum stain 80X.

term acute yellow atrophy is applied when there have been significant amounts of fat present in the liver parenchymal cells, or red atrophy when there has been little fat present. The association of acute atrophy with secondary massive collapse of substantial portions of the parenchyma is known to occur on occasion in cases of hepatitis in which the process is fulminating. Although infectious hepatitis is the most common antecedent to massive collapse, other causes including a variety of hepatotoxins may, on occasion, be responsible. In terms of today's case we are interested in the healing process that occurs in those patients who recover from the acute episode, for, although acute massive necrosis is often fatal, recovery sometimes occurs.

When such livers undergo healing, the predominant process of repair is the formation of regenerative nodules consisting of hepatic parenchymal cells. Marked variation in size of these regenerating nodules is one of the hallmarks of repair (Fig. 7) following massive collapse, and this variation in size appears in part to be related to the amount and location of residual parenchymal elements that serve as sources for regeneration from a few isolated hepatic cells trapped in the collapsed framework and necrotic debris. Larger nodules containing numbers of portal and/or central veins, often in peculiar juxtaposition, originate from confluent or bridging remnants of several adjacent nodules.

I wish to turn our attention momentarily to the nature of the broad bands that separate the regenerating nodules. (Fig. 8.) These so-called fibrous bands of scarring actually consist of a variety of components. In the earlier stages of regeneration they consist principally of the collapsed reticulum framework with varying numbers of portal areas that have survived the necrotizing process. As the process of repair proceeds there is an active proliferation in these areas of structures that resemble bile ducts. Some of these are made up of cells intermediate in appearance between bile duct and hepatic epithelium. The origin of these duct-like structures has not been completely settled although there is strongly suggestive evidence that they

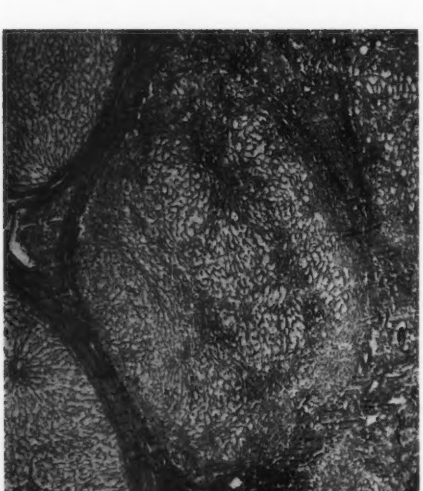

Figure 10
Liver: Multiple foci of regeneration in zone of collapse. Snook reticulum stain 45X.

are derived from hepatic cells rather than representing merely active reparative proliferations of pre-existing bile ducts. Such proliferations are found in a variety of hepatic disorders. A certain amount of fibroblastic activity with secondary fibrocollagenization occurs in these zones that separate the nodules, and this is probably contributed to by the compression of the expanding adjacent nodules. The collapse of reticulum can be beautifully demonstrated by use of a reticulum stain (Fig. 9) with a light counter stain to outline the relationship to the parenchymal cells. The somewhat laminated dark staining strands of reticulum represent an area in which massive or submassive collapse has occurred with subsequent development of a regenerating nodule which, as it expands, adds to the compression effect which we see to be most marked at the immediate periphery of the nodule. The liver cords within the nodule, although showing a somewhat radial arrangement in some areas, suggesting orientation with respect to central veins, show marked disorganization and random arrangement in other portions of the nodule. A similar disorganization is seen here (Fig. 10), where within the central nodule, zones of collapsed reticulum are interspersed with regenerating hepatic cells chaotically arranged. The bizarre alterations of hepatic architecture that may be found in the regenerating nodules following extensive necrosis is well illustrated in this field (Fig. 11) where we find four portal areas in close topographical relationship without any apparent intervening central veins. Although they are not well seen at this 35X magnification, each of the larger vascular spaces seen here was accompanied by a bile duct. A somewhat reversed situation is pictured here (Fig. 12) in that two central veins are in close proximity with absence of any portal triads; another reflection of the distortions of topography that may be found in the reconstructions that follow massive and submassive necrosis and collapse. From these remarks it can be appreciated that the liver in this case is interpreted as representing the entity that is currently most often called post necrotic cirrhosis. That it is one of the forms of cirrhosis is generally accepted.

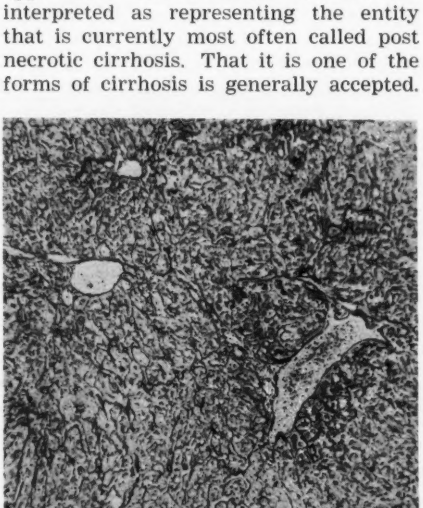

Figure 11
Liver: Four portal areas in close proximity reflecting alteration of liver architecture following collapse. H. & E. 95X.

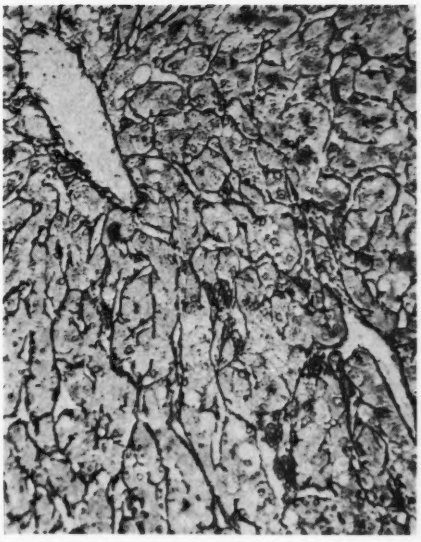

Figure 12

Liver: Two adjacent central veins without intervening portal area. Post collapse with regeneration. H. & E. 250X.

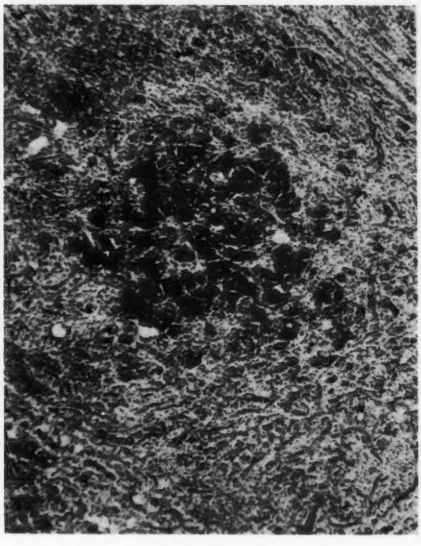

Figure 13

Liver: Fatty change in small regenerating parenchymal nodule. ORO fat stain 105X.

This is reflected in some of the synonyms that may be found in literature such as: coarse nodular cirrhosis, toxic cirrhosis, multilobular cirrhosis, etc. Synonyms such as post necrotic scarring, chronic liver atrophy, and healed acute atrophy place more emphasis upon the original events of necrosis and collapse. It seems most likely that the "large liver" reported at the age of 6 or 7 years probably represented a hepatomegaly associated with an acute infectious hepatitis which progressed to a submassive

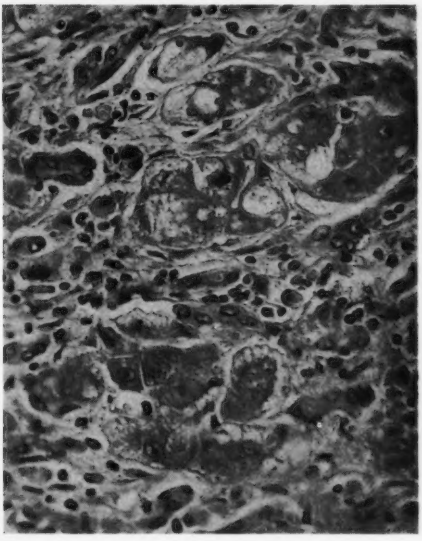

Figure 14

Liver: Hydropic and feathery degeneration of hepatic cells in area of bile stasis. H. & E. 550X.

necrosis with the gradual evolution of the lesion that we recognize here as having both the gross and microscopic characteristics of post necrotic cirrhosis.

The presence of fat globules in hepatic cells in cases of cirrhosis is more characteristic in those of the nutritional or alcoholic type. However, (Fig. 13) although it was not abundant in our case, appreciable amounts of fat were seen in some of the hepatic cell nodules. Such a finding is not unexpected in the presence of the marked anorexia and faulty nutrition that was present in this patient. Other alterations of liver cells

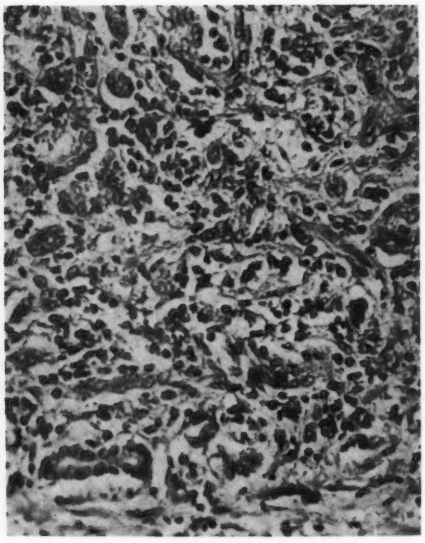

Figure 15
Liver: Acute and chronic inflammatory cell infiltration in connective tissue band. E. & E. 550X.

were seen in some areas. Those which we seen here (Fig. 14) have been described as of frequent occurrence in liver cells in areas of bile stasis (cholestasis). This peculiar vacuolization of some hepatic cells as well as the more delicate rarefaction of the cytoplasm is a combination of hydropic and feathery degeneration. A few plugs of inspissated bile may be seen here in canaliculi. Because of the degree of distortion of the biliary system within the liver in post necrotic cirrhosis, bile stasis occurs in some degree on a mechanical basis and can usually be found without difficulty.

A number of microscopic observations have been made by those interested in the problems of cirrhosis with respect to the progression of the cirrhotic process. It has been felt that if relatively few inflammatory cells were found in the parenchyma and zones of scarring, the cirrhotic process was relatively arrested. The presence of inflammatory cells when found, then argued for an active progression of the cirrhotic process. In our case (Fig. 15) many areas of infiltration by both acute and chronic inflammatory cells were seen, presumably a reflection of an active progression of the cirrhosis. A similar observation has been made for the significance of necrosis, the presence of which is also held to reflect cirrhotic progression. Foci of relatively massive necrosis of nodules were present in our case, and (Fig. 16) in this parenchymal nodule much of the central portion is entirely necrotic. It has been recognized that when hypoxemia develops, perhaps suddenly as the result of a circulatory failure or an acute anemia secondary to severe hemorrhage, necrosis of the parenchymal nodules may supervene quite rapidly. I believe that that is what happened in our case secondary to the massive gastrointestinal hemorrhage the patient had sustained. This combination of hemorrhage and focal hepatic necrosis probably accounts for the three to four-fold increase in white count over the leukopenia that had been previously recorded.

It is remarkable how well the liver of post-necrotic cirrhosis may function. Clinical evidence indicates that this may be for many years. The progressive development of portal hypertension, however, continues and studies of recent

Figure 16
Liver: Large regenerating nodule with acute central necrosis. H. & E. 45X.

years have greatly clarified this process. When the blood vessels of such livers are injected with plastic and studied in three dimensions it is seen that the expanding regenerative nodules exert important pressure effects upon the hepatic venous system. Branches of the hepatic veins appear flattened. This effect is somewhat less upon the portal veins which are more protected by connective tissue and accompanying structures of the portal areas. As fibrosis in the portal areas increases another important alteration of hemodynamics is imposed by the increase in blood flow contributed by the hepatic artery. These are but two of the complex alterations in the circulatory system contributing to portal hypertension that are found in such cirrhotic livers.

In summary then we find this case to represent a late stage of progressive healing and repair of a liver that has undergone extensive necrosis and collapse, probably secondary to an antecedant viral hepatitis. The continuing fibrous scarring associated with regenerating parenchymal nodules of variable size has produced a form of cirrhosis that is termed the post-necrotic type.

FINAL ANATOMICAL DIAGNOSES:

1. Post-necrotic cirrhosis, advanced.
2. Gastric mucosal ulcerations, multiple with massive gastrointestinal hemorrhage.
3. Fibrocongestive splenomegaly.
4. Ascites, massive.
5. Cholemic nephrosis.
6. Testicular atrophy.
7. Gynecomastia, mild.
8. Icterus, generalized.
9. Pulmonary atelectasis, focal.
10. Erythroid hyperlasia of bone marrow.

Chairman: The case is now open for further discussion; Dr. Rappaport.

Dr. Rappaport: I would like to raise another question. Some discussants have suggested that this is a subchronic hepatitis which lasted as long as the clinical history; that is since the beginning of the jaundice. Another discussant suggested that the incident which led to the post-necrotic cirrhosis may have occurred years ago. This point I believe has been clarified by Dr. Bowerman by showing that this is a post necrotic cirrhosis of long standing. With reference to the pancytopenia I would like to say that a thrombocytopenia of 84,000 associated with a neutropenia of about 3,000 can hardly be attributed to secondary hypersplenism unless one is dealing with spleenomegaly of long standing. This might have offered a clue in the differential diagnosis between subacute hepatitis and post necrotic cirrhosis.

Dr. Zimmerman: That certainly makes sense. Hypersplenism resulting from hepatic disease implies chronicity; how chronic a subacute hepatic necrosis has to be, I cannot say.

Dr. Rappaport: I would say you would say you would not expect it after two months. I, at least would not.

Dr. Zimmerman: That is probably true, but it should be verified by studying available cases and reports.

Dr. Rony: I would like to comment, if I may, on what Dr. Bowerman called the endocrine implications in this case. Concerning the minimal gynecomastia that was found at autopsy, one should keep in mind that it is not necessarily an abnormal phenomenon in adolsecent boys. Dr. Young of Northwestern University has made a study of this and found that about 10% of otherwise normal boys of this age have palpable and visible gynecomastia; in a few cases biopsies were made and the histological findings were the same as in this case. Furthermore, if a boy of fifteen dies in a rapidly progressive toxic disease of any kind, some damage to the seminiferous tubules of the testicles with lack of spermatogenesis, as was found in this case, may occur as the result of toxemia.

Chairman: At this age I am very surprised to see no active spermatogenesis. I get the impression it never got going here. As much as we would like to continue to discuss this excellent presentation by our Pathology Department, our time is up and I am afraid we will have to adjourn the meeting.

BOOK REVIEWS

AIDS TO MEDICAL DIAGNOSIS. G. E. F. Sutton. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. 399 pages.

In this unique handbook of medicine, 399 pages in length, the author has attempted to include all the major diseases of the various systems. Implicit in such a brief handbook is a lack of reference to specific treatments, but a fair degree of success is achieved with respect to the clear and concise enumeration of important signs, symptoms, and laboratory, confirmation in diagnosis and differential diagnosis. While not recommended as a basic text of medicine, it nevertheless deserves consideration as a source for the neophyte seeking a rapid reference and quick insight into an unfamiliar problem.

—A.G.

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ILLUSTRATED PREOPERATIVE AND POSTOPERATIVE CARE, by Philip Thorek, M.D. Ninety-eight pages with 60 illustrations by Carl L. Linden, Assistant Professor of Merical Illustration, University of Illinois School of Medicine. Philadelphia, J. B. Lippincott Company, 1958. $5.00.

This small text is divided into two sections, preoperative and postoperative. The former traces the evolution of the patient from the first visit to the surgeon until surgery is performed. It includes a very brief summary of the most fundamental methods of evaluating diet, heart, lungs and kidney function. It lists the laboratory tests the author considers routine for every surgical patient as well as some of the indications for further studies of the various systems. Bleeding and clotting time are not included in the routine list.

The latter half of the book is concerned with postoperative care. It is divided into many sections such as the immediate postoperative period, the recovery room, parenteral fluids, acidosis and alkalosis, fever, bowel distention, thrombophlebitis, eveseration, paratotis and shock. The sections are short and to the major point.

A volume of this size is, of course, limited in the information it imports. The major advances in preoperative and post operative care are enumerated in an easily and rapidly readable (1 hour) fashion. The pictures are well done, but lend very little to the text. The strongest point of this volume is the section on postoperative fluids. Students and those not regularly in contact with surgical patients will find this volume a useful and rapid introduction or review.

—J.S.

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GRANT'S METHOD OF ANATOMY, G. E. F. Sutton. The Williams & Wilkins Co., Baltimore, 838 pages.

The 6th edition of *Grant's Method of Anatomy* has been revised throughout. New material has been added, particularly on matters of clinical importance, such as the mechanics of the foot, the lubrication of joints, the neurovascular hilia of muscles, electromyography, the segments of the liver, the lymphatics, the eruption of teeth, and recent information on the fusion times of epiphyses. In addition, a favorable deletion has been made; namely the omission of descriptions of microscopic structures.

In conclusion, we feel that this book serves its purpose as a working instrument designed to make Anatomy rational, interesting, and of direct application to the problems of medicine and surgery.

—J.I.D.

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UROLOGY IN GENERAL PRACTICE, Frank C. Hamm, M.D., F.A.C.S. and Sidney R. Weinberg, M.D., F.A.C.S. J. B. Lippincott Company, Philadelphia, Pennsylvania. 287 pages.

This paperback edition is designed for a reference book for medical students and physicians in other branches of medicine. Though it does fulfill its stated purpose well, it is not recommended to Urologists and residents in urology.

The principles followed are generally those which apply to surgery in general. However, emphasis on special techniques such as cystoscopy are included. Bibliographies are supplied at the end of each chapter for those who wish to pursue certain topics further. The illustrations are very helpful.

—M.K.